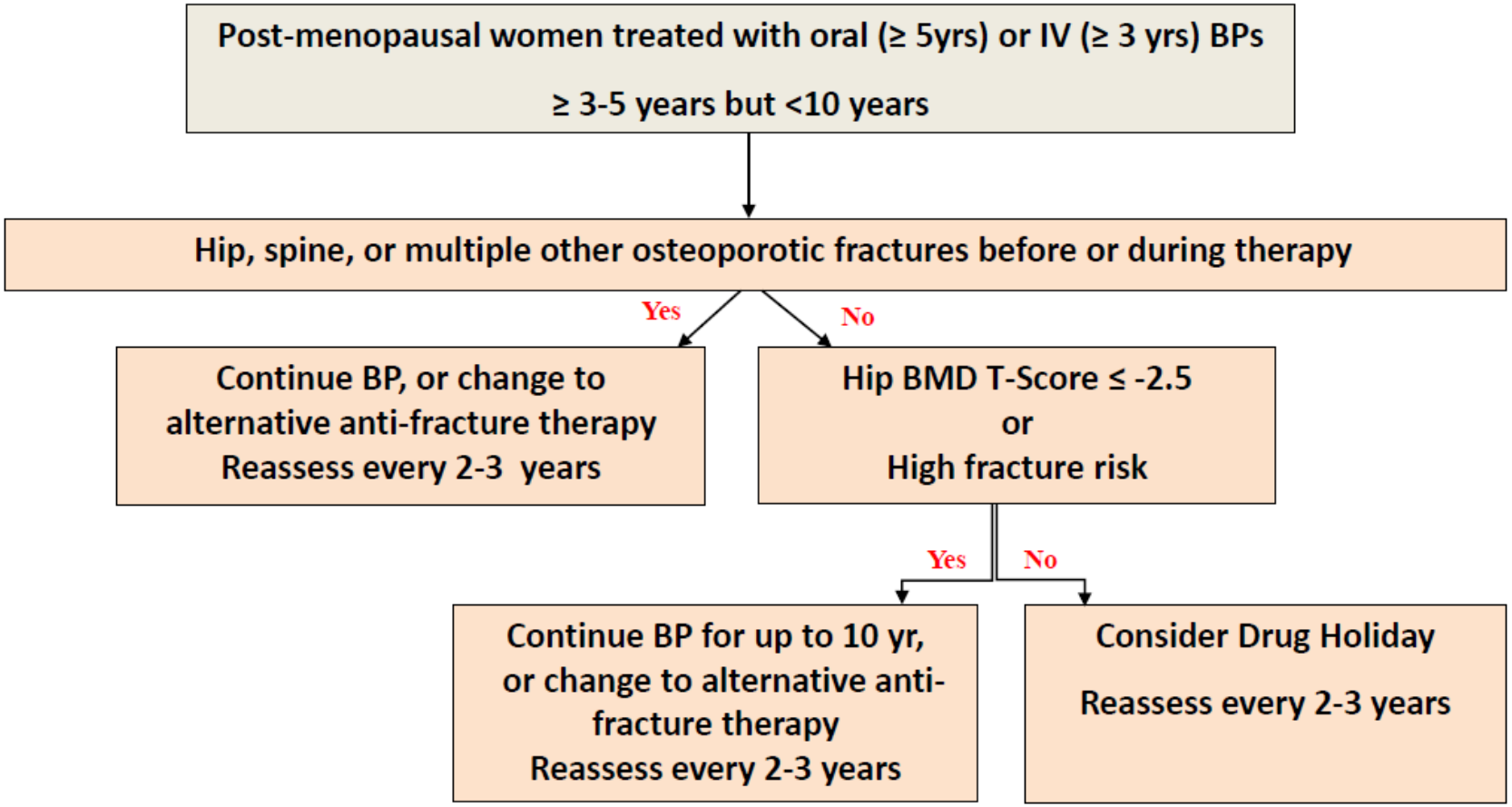
Σημαντικότερες ανακοινώσεις ASBMR 2018

Συμεών Τουρνής
Ενδοκρινολόγος
ΕΕΠΜΣ ΕΚΠΑ
Νοσοκομείο Κατ

Διφωσφονικά

- Διακοπή BSP
  - Μείωση κίνδυνου AFF
  - Κίνδυνος καταγμάτων ισχίου
- Σχέση TH BMD και AFF

Algorithm for Management of Postmenopausal Women on Long Term Bisphosphonate Therapy



ASBMR Long Term BP Task Force

REVIEW

JBMR®

Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Second Report of a Task Force of the American Society for Bone and Mineral Research

Journal of Bone and Mineral Research, Vol. 29, No. 1, January 2014, pp 1–23

Table 3. ASBMR Task Force 2013 Revised Case Definition of AFFs

To satisfy the case definition of AFF, the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.
In addition, at least four of five Major Features must be present. None of the Minor Features is required but have sometimes been associated with these fractures.
Major features[a]
The fracture is associated with minimal or no trauma, as in a fall from a standing height or less
The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
The fracture is noncomminuted **or minimally comminuted**
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")
Minor features
Generalized increase in cortical thickness of the **femoral diaphyses**
Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
Bilateral **incomplete or complete femoral diaphysis fractures**
Delayed **fracture** healing

1005

Do Drug Holidays Reduce Atypical Femur Fracture Risk?: Results from the Southern California Osteoporosis Cohort Study (SOCS) Annette L. Adams*[1], Bonnie H. Li[1], Denison S. Ryan[1], Erik J. Geiger[2], Richard M. Dell[1], Dennis M. Black[2]. [1]Kaiser Permanente Southern California, United States, [2]University of California, San Francisco, United States

Long-term bisphosphonate (BP) use has been associated with increased risk of atypical femur fractures (AFF). BP holidays of 3-5 years have been recommended as a way of balancing the risk of AFF with the intended anti-fracture benefit of the medications, and studies have suggested that women who discontinue BP after 3-5 years of use are not at increased risk for osteoporosis-related fractures. However, whether AFF risk is lowered after discontinuation of BP is uncertain. To address the relationship of time since last BP use and risk of AFF, we conducted a cohort study of women aged ≥50 years who were members of Kaiser Permanente Southern California (KPSC) during the period 1/1/2007-9/30/2015. Women were required to have pharmacy benefits and to have been members of KPSC for ≥1 year prior to cohort entry. We included in the cohort any woman who had used a BP and had at least one available pre-treatment bone mineral density (BMD) total hip scan. AFFs were identified and verified by physician review of x-ray images for fractures occurring during the study period with ICD-9 diagnosis codes for subtrochanteric or femoral shaft fractures. Women were considered to have discontinued BP if there was a gap >3 months between last BP use and cohort entry anniversaries. We also included information on the following potential confounders of the association between time since discontinuation and AFF: age, race/ethnicity, smoking, height, fracture history, duration of BP use, duration of glucocorticoid use, and pre-treatment total hip T-score. Multivariable time-varying Cox proportional hazards methods were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). The cohort included 152,934 women meeting inclusion criteria with 185 AFF (incidence rate 1.70 per 10,000 person-years). After adjustment for all confounders, there was a 44% reduction in the risk of AFF in the first year after discontinuation compared to women who continued to use BP (HR 0.56, CI 0.38-0.82). In years 1 to 4 after discontinuation, AFF risk was decreased by 80% (HR 0.20, CI 0.10-0.37) and after >4 years, AFF risk was reduced by 78% (HR 0.22, CI 0.08-0.59) compared to current users. These results suggest that among women with BP use of varying duration, discontinuation is associated with substantially decreased risk of AFF. Thus, these results suggest that a drug holiday of 3-5 years would likely markedly reduce AFF risk among long-term BP users.

*Disclosures: **Annette L. Adams**, Merck, Grant/Research Support*

1005: BSP holiday and AFF

- Σχεδιασμός: Cohort study
- Πληθυσμός: 152,934 Γυναίκες > 50 ετών υπό BSP (Kaiser Permanente Southern California) (KPSC)
- 188 AFF (επίπτωση 1,7 per 10,000 person yrs)
- Διάρκεια: 1/1/2007-30/9/2015 (7.75 yrs)
- Έλεγχος για age, race/ethnicity, smoking, height, fracture history, duration of BP use, duration of glucocorticoid use, and pre-treatment total hip T-score
- 1 έτος διακοπής : ↓ 44%, HR 0.56, CI 0.38-0.82
- 1-4 έτη διακοπής : ↓ 80%, HR 0.20, CI 0.10-0.37
- > 4 έτη διακοπής : ↓ 78%, HR 0.22, CI 0.08-0.59

Συμπέρασμα

These results suggest that among women with BP use of varying duration, discontinuation is associated with substantially decreased risk of AFF. Thus, these results suggest that a drug holiday of 3-5 years would likely markedly reduce AFF risk among long-term BP users.

1007

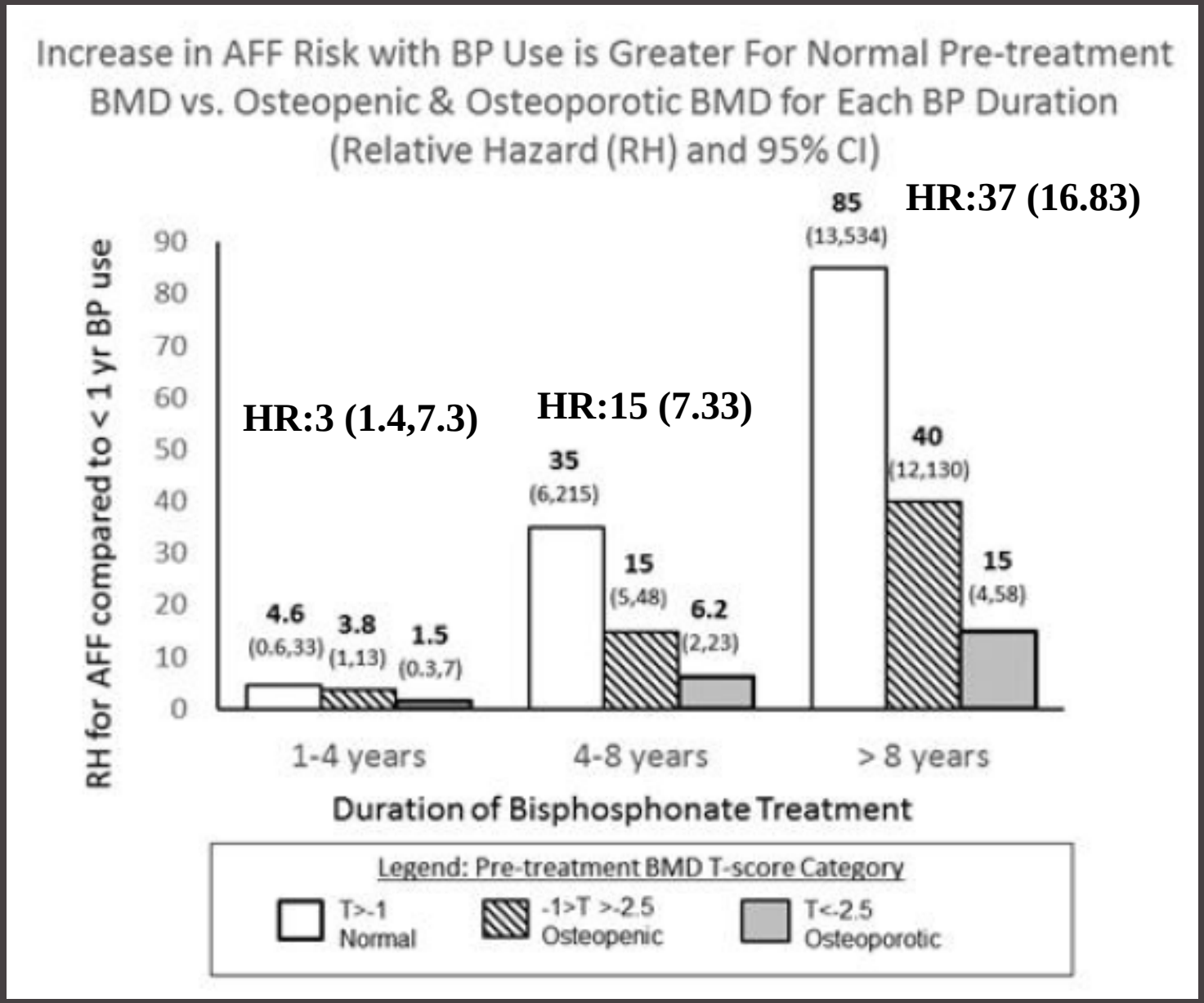
Bisphosphonate Use and Risk of AFF Varies by Pre-treatment BMD Level: Results from the Southern California Osteoporosis Cohort Study (SOCS)

Dennis M. Black*[1], Erik J. Geiger[1], Bonnie H. Li[2], Denison S. Ryan[2], Richard M. Dell[2], Annette L. Adams[2]. [1]University of California, San Francisco, United States, [2]Kaiser Permanente Southern California, United States

While most studies have shown bisphosphonate (BP) use and longer duration is associated with increased atypical femur fracture (AFF) risk, the effect might be attenuated if indications for BP treatment, such as BMD, could be controlled. However, no AFF studies have included pre-BP BMD. To test if pre-treatment BMD attenuates the relationship of BP duration to AFF risk, we analyzed data from Kaiser Permanente Southern California (KPSC), an HMO with ~4.5 million members. We established a cohort of women >50 yrs with cohort entry from 1/1/2007-9/30/15. We assessed all X-rays with ICD9 coded subtrochanteric or femoral shaft fractures using ASBMR 2014 criteria with verified adjudication by 2 experts. Risk factors including age, Asian race, pretreatment BMD (PT BMD), BP use, fracture hx, height, GC use and smoking hx were available for up to 10 years prior to cohort entry and were updated annually thereafter. PT BMD was defined as total hip BMD before or soon after starting BPs. The relationship of BP duration to AFF risk was assessed before and after inclusion of PT BMD in multivariable (MV) Cox models with time-varying covariates. This analysis included women who had both PT BMD and any BP use (N=152,934). There were 185 AFFs overall. In a MV model (without PT BMD), those with longer BP duration had higher AFF risk. Compared to <1 year BP the relative hazard (RH) for 1-4 yrs of BP use was 3(CI 1.4,7.3), for 4-8 yrs was 15(CI 7,33) and >8 yrs was 37(CI 16,83). PT BMD added to the model did not attenuate the relationship of BP duration to AFF risk. Inclusion of PT BMD also showed those with higher BMD had a 40%. AFF risk per SD BMD increase (HR 1.4(CI 1.2 1.7)). To further study PT BMD and AFF, we performed analyses stratified by PT BMD T-score (T>-1;-1 to -2.5;T<-2.5). We consistently observed larger risk increases with BPs for those with higher PT BMD (Figure). For example, in those with normal PT BMD (T>-1) the RH for 4-8 years BP use (vs<1 yr) was 35 compared to 15 in those with osteopenic BMD and compared to 6 in those with osteoporotic BMD (T<-2.5). We conclude that adjustment for PT BMD did not attenuate the relationship of BP use to AFF risk. Surprisingly, our results indicate that women with higher PT BMD have a larger increase in AFF risk with BP use than those with lower BMD. If confirmed in other studies, these results suggest that PT BMD could impact clinical decisions around patient selection for BP initiation and drug holidays.

1007: Pre-T total hip BMD and AFF

- Σχεδιασμός: Cohort study
- Σκοπός: Η διερεύνηση της επίδρασης της οστικής πυκνότητας στο συνολικό ισχίο, πριν την έναρξη αγωγής με BSP, στον κίνδυνο εμφάνισης AFF
- Πληθυσμός: 152934 Γυναίκες > 50 ετών υπό BSP (Kaiser Permanente Southern California) (KPSC)
- 185 AFF
- Έλεγχος: age, Asian race, pretreatment BMD, BP use, fracture hx, height, GC use and smoking
- Διάρκεια: 1/1/2007-30/9/2015 (7.75 yrs)



Για κάθε 1 SD αύξηση της BMD ΤΗ αυξάνεται ο κίνδυνος AFF κατά 40%

Συμπέρασμα

We conclude that adjustment for PT BMD did not attenuate the relationship of BP use to AFF risk.

Surprisingly, our results indicate that women with higher PT BMD have a larger increase

in AFF risk with BP use than those with lower BMD. If confirmed in other studies, these

results suggest that PT BMD could impact clinical decisions around patient selection for BP

initiation and drug holidays.

1006

The Impact of Bisphosphonate Drug Holidays on Fracture Rates

Jeffrey Curtis*, Rui Chen, Zixu Li, Tarun Arora, Kenneth Saag, Nicole Wright, Shanette Daigle, Meredith Kilgore, Elizabeth Delzell. University of Alabama at Birmingham, United States

IntroductionDiscontinuation of bisphosphonates after at least 3-5 years of continuous therapy is becoming increasingly common in the U.S. However, the benefits and risks of stopping bisphosphonates (BPs), and the timing as to when it might be optimal to restart, are unclear. We conducted a population-based cohort study of women on long term BP therapy to evaluate the rate of hip fracture following a drug holiday (temporary or permanent BP discontinuation).MethodsMedicare data (2006-2015) were used to identify all women with medical and pharmacy coverage who initiated a BP and were at least 80% adherent for at least 3 years ("baseline"), at which time follow-up began. Patients using other bone therapies (e.g. denosumab, estrogen, teriparatide, calcitonin) were excluded (or censored, if they started after follow-up began). Subgroups defined by exclusive use of specific BPs, and prior fragility fracture, were defined.Crude rates of hip and other types of fractures using validated algorithms were evaluated in relation to continuing BP therapy vs. stopping, and time since stopping. Cox proportional hazards ratios (HRs) evaluated the adjusted risk of stopping for more than 2 years compared to continued use, controlling for potentially confounding factors.ResultsA total of 160,369 women were eligible for analysis, and 36% underwent a BP drug holiday of >12 months. Overall, during a median (IQR) follow-up of 2.7 (1.5, 4.1) years, there were 4,823 hip fractures. Compared to continued BP use, hip fracture rates were significantly elevated among women undergoing BP drug holidays. Adjusted HRs for the association between drug holiday >2y and hip fracture are shown overall and for key subgroups (Table). Risk was similarly elevated for humerus fractures but not for other fracture types.ConclusionsIn a large cohort of older U.S. women, a BP drug holiday greater than 2 years was associated with a significantly increased risk for hip fracture but was minimally elevated for other fracture types.

1006: BSP holiday and hip fractures

- Σχεδιασμός: Cohort study
- Πληθυσμός: 160,369 Γυναίκες > 50 ετών υπό BSP, adherent > 80% την τελευταία 3 ετία , 36% έκαναν διακοπή για > 12 μήνες
- Σύγκριση μεταξύ διακοπής για τουλάχιστον 2 έτη vs. continued use
- 4823 hip fractures
- Διάρκεια follow - up: 2.7 yrs (1.5, 4.1)

Cohort	Women, n	Number of hip fractures, n	Crude Incidence Rate per 1000 person-years	Adjusted* Hazard Ratio (95% CI)
Any BP	160,369	4,823	14.0	1.22 (1.11 – 1.34)
Alendronate users	81,287	2,245	13.1	1.28 (1.12 – 1.46)
Risedronate users	9,823	269	13.8	1.45 (1.00 - 2.11)
Zoledronate users	13,885	367	18.0	1.31 (0.94 - 1.82)
Prior fragility fracture	6,914	430	37.4	1.38 (1.01 – 1.89)

*Hazard ratio for women with a drug holiday of >2 years compared to persistent users, adjusted for age, region, race, rural or urban, median income, calendar year of study entry, comorbidity (fragility fracture, Charlson comorbidity index), DXA, office visits, office visits with bone specialists, long term care residence, vitamin D deficiency, glucocorticoids, and other factors, assessed…

BSP

- Ο κίνδυνος εμφάνισης AFF υπό BSP αυξάνεται με τη μεγαλύτερη διάρκεια λήψης του BSP.
- Ο κίνδυνος είναι μεγαλύτερος όσο μεγαλύτερη είναι η BMD εκκίνησης στο συνολικό ισχίο
- Η διακοπή των BSP για περισσότερο από 2 έτη συνοδεύεται από αύξηση του κινδύνου κατάγματος ισχίου (28-45%)

LB-1167

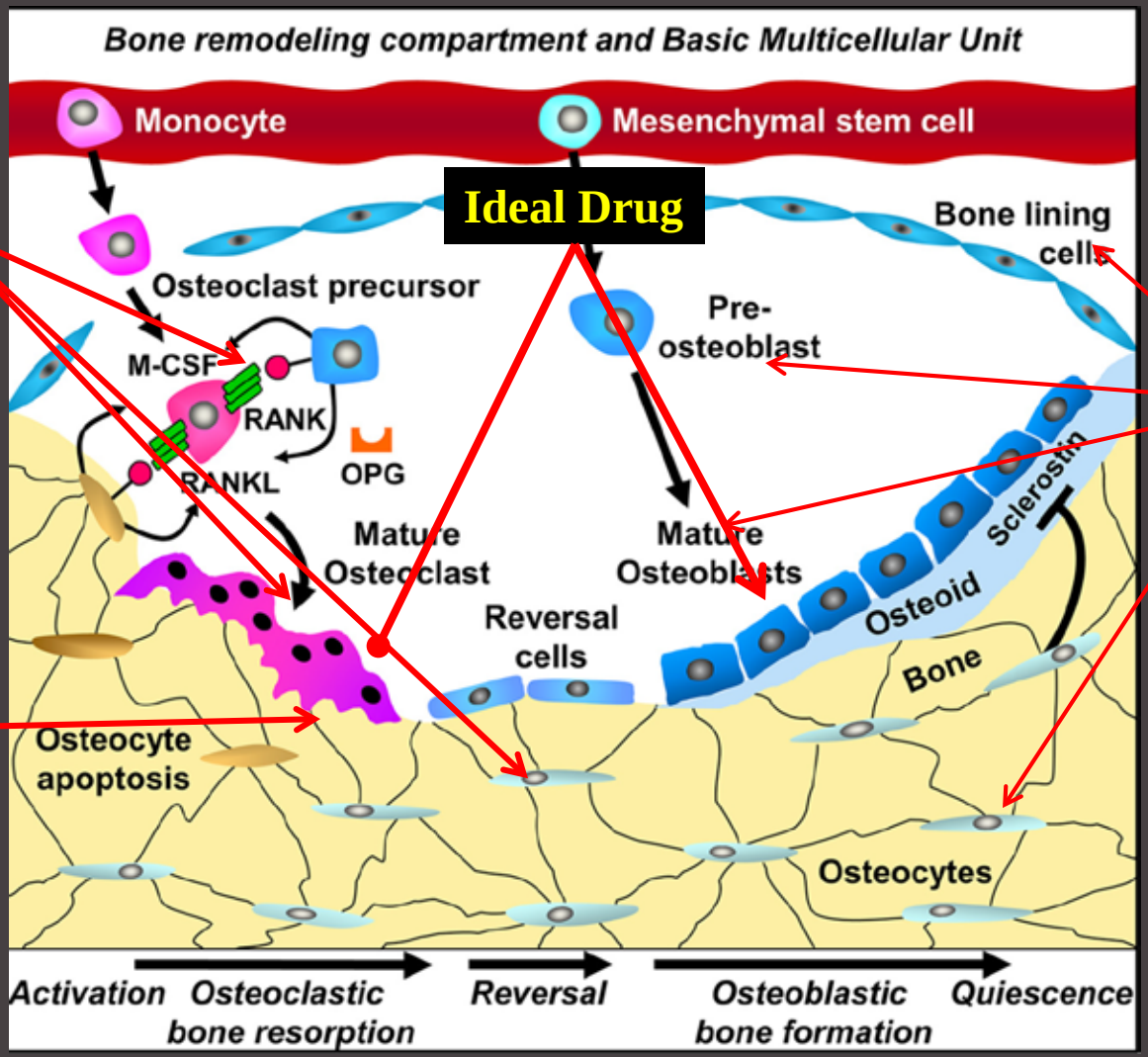
Fracture Risk after Stopping Adjuvant Denosumab in Hormone Receptor Positive Breast Cancer Patients on Aromatase Inhibitor Therapy – an Analysis of 3,425 Postmenopausal Patients in the Phase III ABCSG-18 trial

Georg Pfeiler*[1], Guenther G. Steger[2], Daniel Egle [3], Richard Greil [4], Florian Fitzal [5], Viktor Wette [6], Marija Balic [7], Ferdinand Haslbauer [8], Elisabeth Melbinger-Zeinitzer [9], Vesna Bjelic-Radisic [10], Jonas Bergh [11], Raimund Jakesz [5], Christian Marth [3], Paul Sevelda [12], Brigitte Mlineritsch [13], Ruth Exner [5], Christian Fesl [14], Sophie Frantal [14], Christian F Singer[1], Michael Gnant [5]. [1]Medical University of Vienna/ Department of Obstetrics and Gynecology and Comprehensive Cancer Center, Austria, [2]Medical University of Vienna/ Department of of Internal Medicine I/Oncology, Austria, [3]Medical University Innsbruck/ Department of Gynecology, Austria, [4]Paracelsus Medical Univerity Salzburg/ Department of Internal Medicine III and Salzburg Cancer Research Institute, Austria, [5]Medical University of Vienna/ Department of Surgery and Comprehensive Cancer Center, Austria, [6]Breast Center St. Veit/ Glan/ Doctor´s Office Wette, Austria, [7]Medical University Graz/ Department of Oncology, Austria, [8]Hospital Vöcklabruck/ Department of Internal Medicine, Austria, [9]Hospital Wolfsberg/ Department of Surgery, Austria, [10]Medical University Graz/ Department of Gynecology, Austria, [11]Department of Oncology-Pathology, Karolinska Institutet and Cancer Theme, Karolinska University Hospital, 17176-Stockholm, Sweden, [12]Karl Landsteiner Institute for Gynecologic Oncology and Senology, Austria, [13]Paracelsus Medical Univerity Salzburg/ Department of Internal Medicine III, Austria, [14]Austrian Breast & Colorectal Cancer Study Group/ Statistic Department, Austria

ABCSG-18 trial

- In the prospective, double-blind, placebo-controlled phase III
- 3,425 postmenopausal HR+ patients treated with adjuvant AI to denosumab 60mg or placebo s.c. q6 months until the prespecified number of 247 first clinical fractures was reached.
- Διακοπή AI
  - 2,451 patients later than 6 months after the last dose of denosumab/placebo.
  - 387 patients prior to last dose
  - 295 patients within 6 months after the last dose of denosumab/placebo.
- Follow-up after stopping: 36 months
- Fractures: 318 fr/ 199 pts (incidence rate 6.2%)
  - Total 163/98 (dmab) vs 155/101 (pl)
  - Clinical: 39/22 vs. 14/9, HR 2.44 (1.12-5.32)
  - Multiple: 28/11 vs. 8/3, HR 3.52 (0.98-12.64)
- Η αύξηση των κλινικών και πολλαπλών σπονδυλικών καταγμάτων παρατηρήθηκε σε ασθενείς που διέκοψαν τη θεραπεία με AI πριν ή μετά του 6 μήνες από την τελευταία δόση του Dmab, και όχι στις ασθενείς που διέκοψαν την θεραπεία με AI εντός του εξαμήνου.
- Conclusion: **Rebound- associated fractures after termination of adjuvant denosumab therapy may be avoided when stopping bone-compromising AI therapy within 6 months**

Combination Therapy



Dmab

↓ AcF
↓ BF
↓ BR

BSP

TPTD

↑ AcF
↑ BF
↑ BR

High dose Teriparatide + Dmab

1073

Rapid and Large BMD Increases in Postmenopausal Women Treated With Combined High-Dose Teriparatide and Denosumab: The DATA-HD Randomized Controlled Trial

Benjamin Leder*[1], Hang Lee[2], Natalie David[2], Richard Eastell[3], Tsai Joy[2]. [1]Harvard Medical School. Massachusetts General Hospital, United States, [2]Massachusetts General Hospital, United States, [3]Mellanby Centre for Bone Research, United Kingdom

In the DATA study, we demonstrated that when given concomitantly, denosumab (DMAB) fully inhibits teriparatide (TPTD)-induced bone resorption while allowing for continued TPTD-induced modeling-based bone formation. These effects on bone turnover, in turn, result in greater gains in hip and spine BMD than can be achieved with either drug alone. We thus hypothesized that combining DMAB with a larger anabolic stimulus, in the form of high-dose TPTD, would further expand the separation between rates of bone formation and resorption and result in even larger and faster increases in bone mass. Methods: 69 postmenopausal osteoporotic women (age 52-83) were randomized to one of two treatments: TPTD 40-mcg (high dose-HD) or TPTD 20-mcg (standard dose-SD) given months 0-9 overlapped with DMAB 60-mg SC given months 3-15 for a total study duration of 15 months. Subjects were excluded for oral BP exposure within 6 months or any exposure to TPTD, DMAB, or IV BPs. Results: At month 15, mean total hip (TH) BMD increased more in the HD (6.1 ± 3.4%) than the SD group (3.9 ± 2.9%, P<0.001). Femoral neck (FN) BMD also increased more in the HD than SD group (6.8 ± 4.1% vs 4.3 ± 3.7%, P=0.04) as did spine BMD (17.5 ± 6.0% vs 9.5 ± 3.2%, P<0.001). Of note, both TH and FN BMD had increased by >5% and spine BMD by >14% by month 9 (after only 3 months of TPTD followed by 6 months of combined therapy). Additionally, the relative greater BMD gains in the HD vs the SD group continued to expand during the final 6-months of treatment despite the fact that both groups were receiving identical DMAB monotherapy during this phase.In the initial 3-months of TPTD monotherapy, serum bone formation markers increased significantly more in the HD than SD group (P1NP, 402% vs 153%, OC 254% vs 140%.), as did bone resorption (CTX, 159% vs 84%). At month 9, OC remained above baseline in the HD but not SD group (+10% vs -27%) and P1NP was significantly less suppressed in HD than SD (-32% vs -43%). CTX was also less suppressed in the HD than SD group (-46% vs -69%). Month-15 bone turnover markers (after 6 months of DMAB monotherapy) were similarly suppressed in both groups. Summary: The combination of TPTD 40-mcg and DMAB increases hip and spine BMD faster and more than standard combination therapy or any available single drug. These robust and rapid increases in BMD suggest that by expanding the separation between bone formation and bone resorption, the HD regimen may provide the fastest means of restoring skeletal integrity in osteoporotic patients at the highest risk of fragility fracture. Larger trials are urgently needed to fully evaluate the efficacy and safety of this treatment approach.

1059

Effect of Denosumab and High-Dose Teriparatide on Peripheral Bone Mineral Density and Microarchitecture Joy Tsai*[1], Amy Yuan[1], Natalie David[1], Hang Lee[1], Mary Bouxsein[2], Benjamin Leder[1]. [1]Massachusetts General Hospital, United States, [2]Beth Israel Deaconess Medical Center, United States

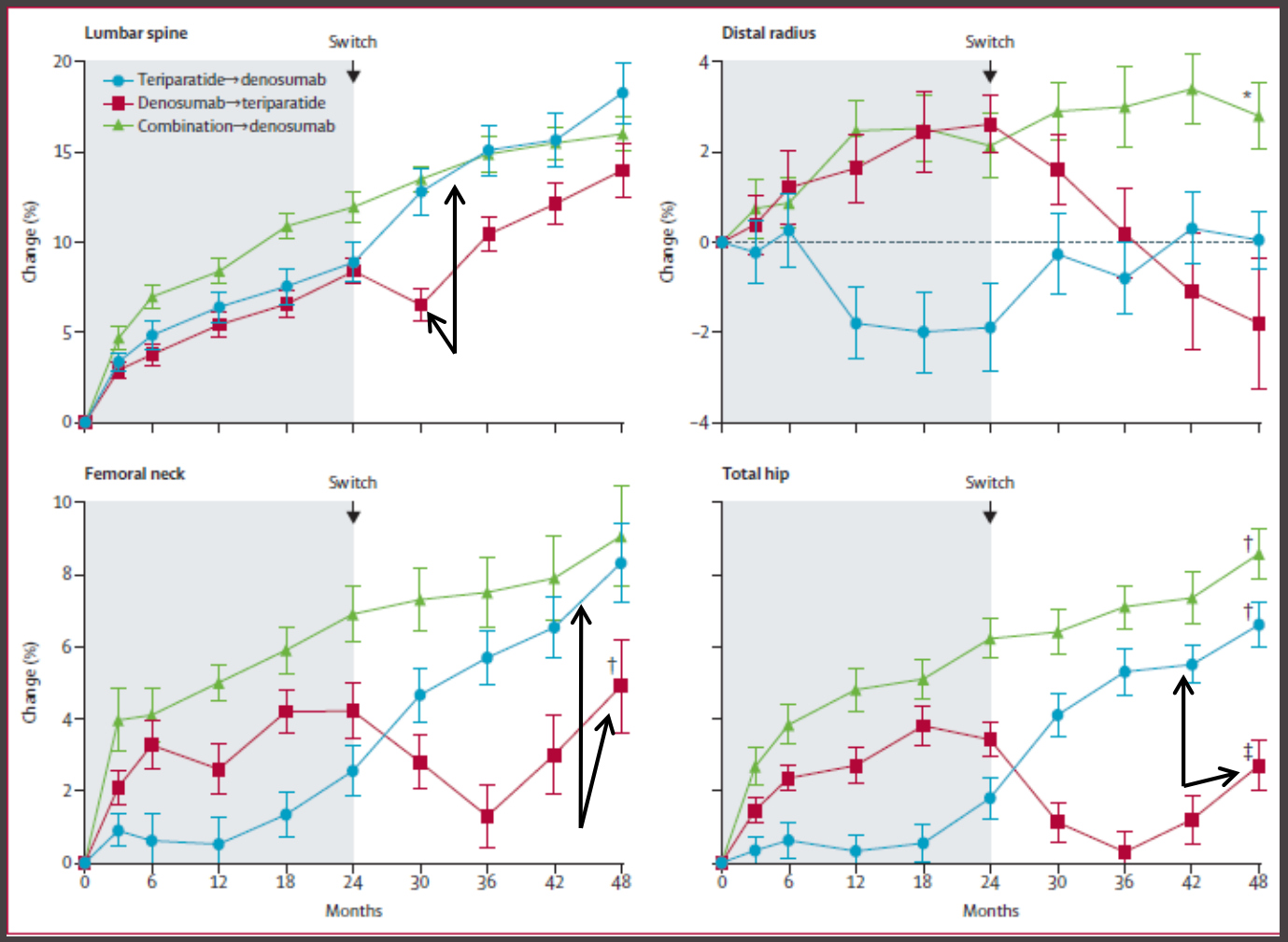
Background: In postmenopausal women with osteoporosis, 15 months of combined denosumab (DMAB) and high-dose (HD) teriparatide (TPTD) increases bone mineral density (BMD) at the spine and hip more and faster than combined DMAB and standard-dose (SD) TPTD. The effects of combined DMAB and HD TPTD on peripheral volumetric BMD and microarchitecture are unknown. Methods: We randomized 69 postmenopausal women ages 52-83yo at high fracture risk to 1 of 2 groups: TPTD 20-mcg (SD) or TPTD 40-mcg QD (HD) given months 0-9 overlapped with DMAB 60-mg SC Q6M given months 3-15. Women were excluded if they ever received IV bisphosphonates (BP) or oral BPs within 6 months. Total, trabecular, & cortical density (Tt.vBMD, Tb.vBMD, Ct.vBMD); trabecular thickness, spacing, & number; and cortical thickness & porosity (Ct.Th, Ct.Po) were measured by high-resolution peripheral QCT of the distal tibia and radius. Results: Tt.vBMD at the tibia increased more in the HD (5.3±5.4%) than the SD group (3.4±1.9%) (p=0.01). Tt.vBMD also increased more in the HD group (2.6±4.4%) than the SD group (1.0±4.5%) at the radius, but this did not meet statistical significance (p=0.06). Ct.vBMD at the tibia increased by 2.2±1.8% in the HD group compared to 1.6 ± 1.5% in the SD group (p=0.13) whereas at the radius Ct.vBMD in the HD group increased by 1.0±2.2% which was significantly greater than the increase in the SD group (0.3±1.5%) (p=0.047). Changes in Tb.vBMD at both the tibia and the radius showed a similar pattern but between group comparisons were not significant. Tb.vBMD at the tibia increased by 1.7±2.0% in the HD group and by 1.2±2.2% in the SD group (p=0.17) whereas at the radius Tb.vBMD increased by 2.2±4.0% in the HD group and by 1.2±4.2% in the SD group (p=0.14). Ct.Po did not increase in either group at the tibia or the radius and there were no between group differences. Conclusions: The TPTD 40-mcg/DMAB combination increases Tt.vBMD at the radius and tibia and Ct.vBMD at the radius more than TPTD 20-mcg/DMAB combination. Moreover, in contrast to the well-described decrease in Ct.vBMD and increase in Ct.Po that is observed with TPTD alone, co-administration of DMAB prevents these deleterious changes even when TPTD is given in double the standard dose. These results show that the HD combination results in more favorable changes in both trabecular and cortical peripheral bone than does the SD combination and may be a useful therapy in patients at high risk of fragility fracture.

Dmab followed by TPTD and vice versa

Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial

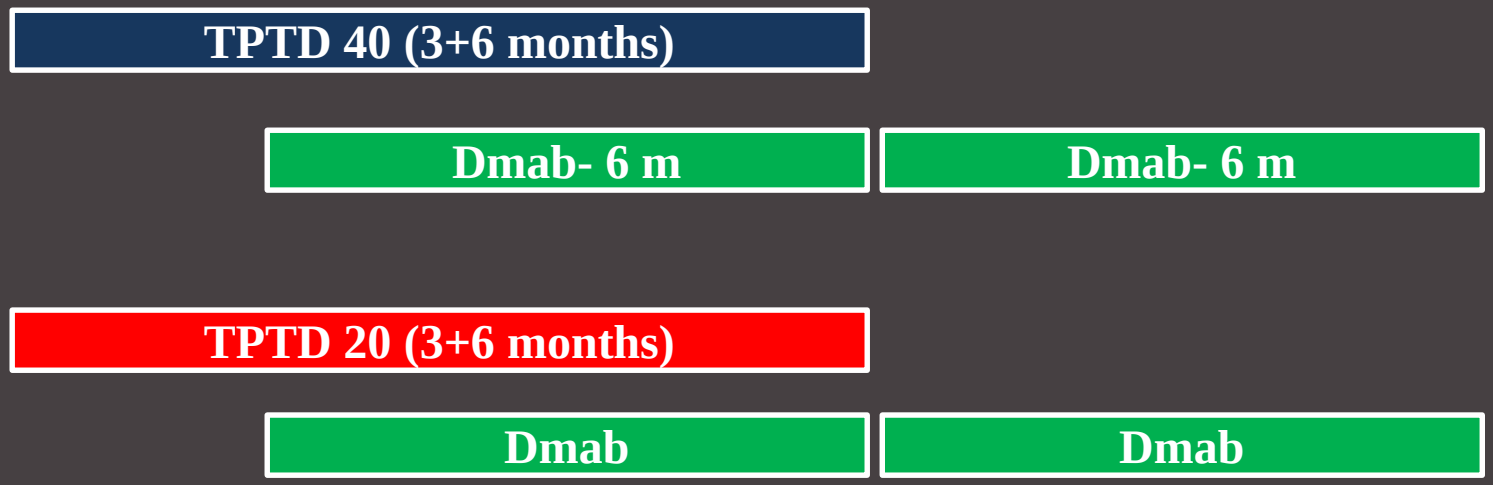
Benjamin Z Leder, Joy N Tsai, Alexander V Uihlein, Paul M Wallace, Hang Lee, Robert M Neer, Sherri-Ann M Burnett-Bowie

Lancet 2015

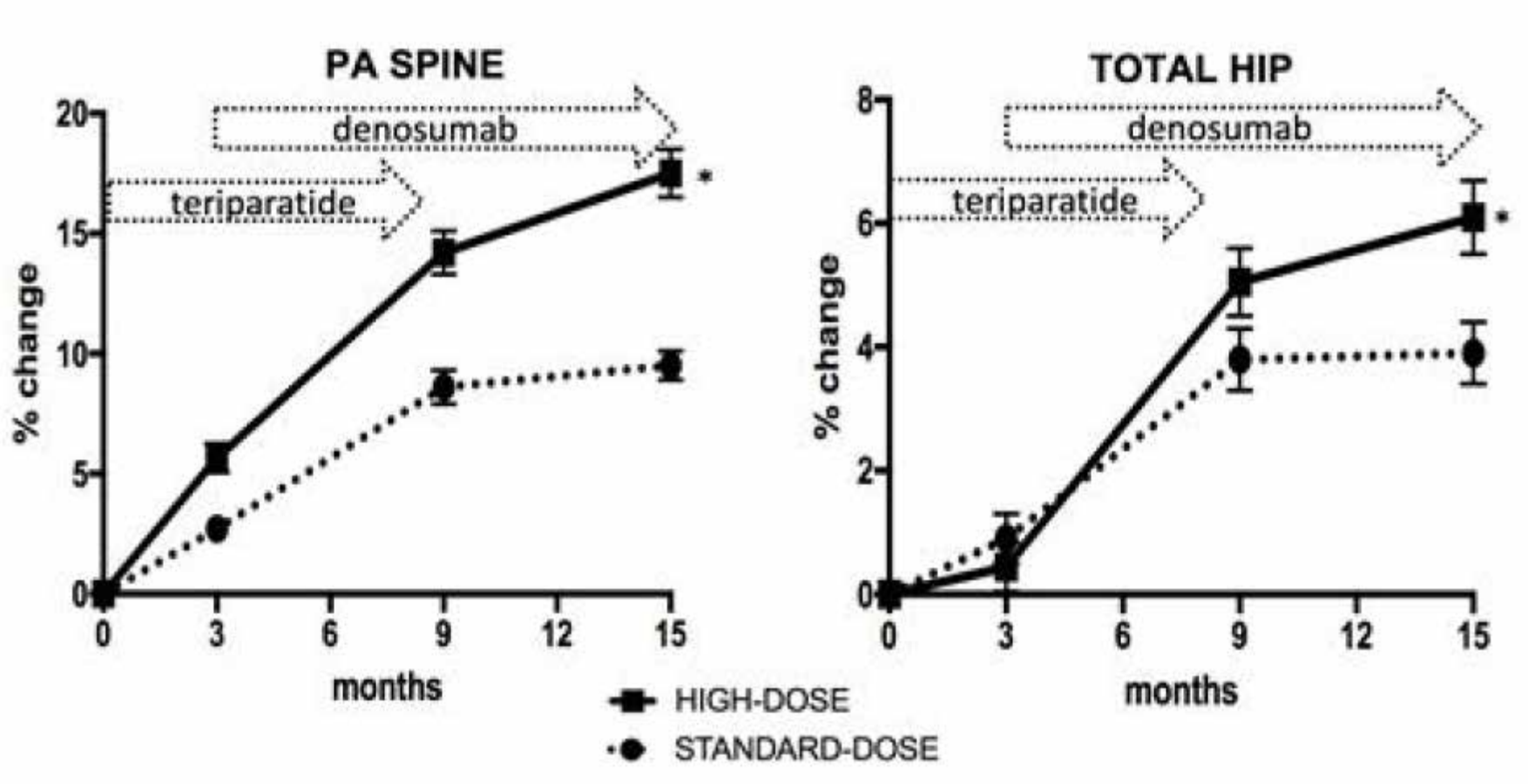


Σχεδιασμός της Μελέτης

- 69 γυναίκες
- Ηλικία 52-83
- DXA LS, Hip
- HRpQCT tibia & radius



Αποτελέσματα DXA



Αποτελέσματα hrpQCT

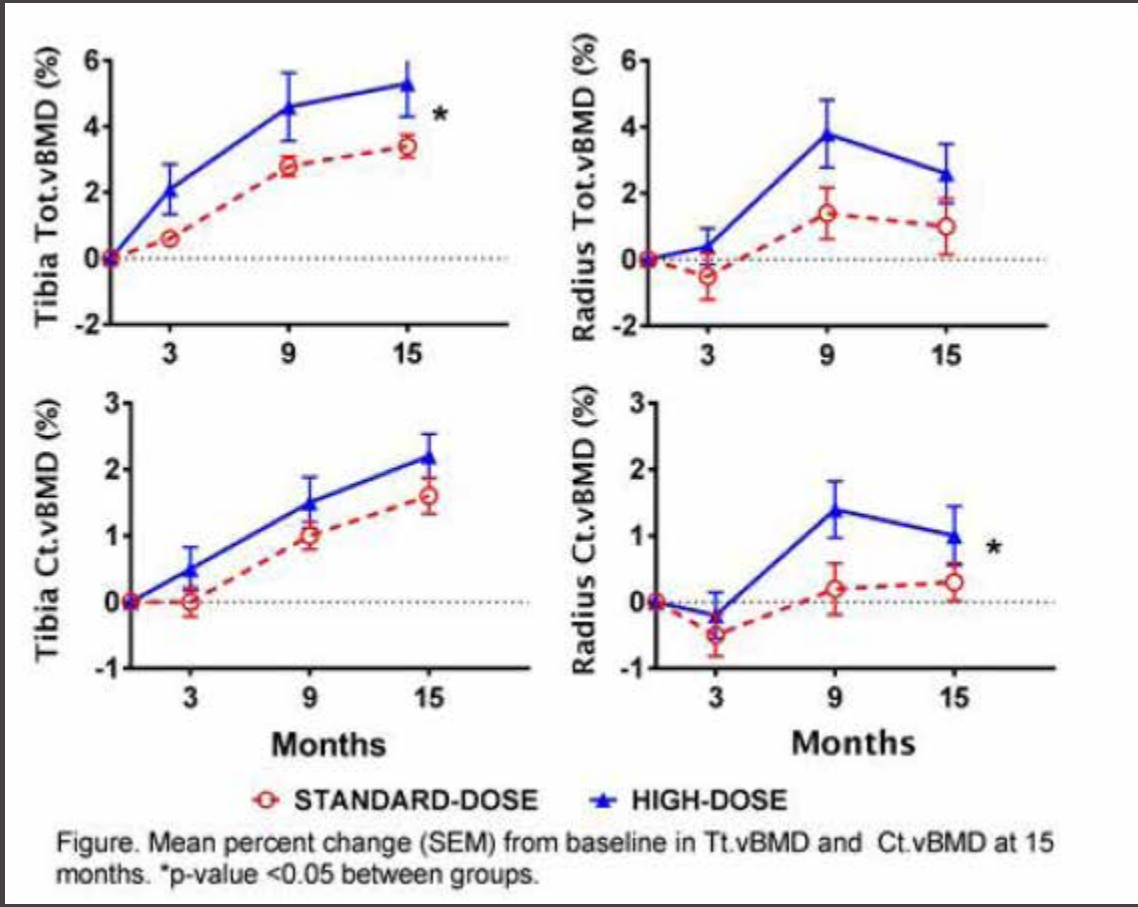


Figure. Mean percent change (SEM) from baseline in Tt.vBMD and Ct.vBMD at 15 months. *p-value <0.05 between groups.

	TPD40+Dmab	TPD20+Dmab	p
LS	17.3 ± 6	9.5 ± 3.2	0.001
FN	6.8 ± 4.1	4.3 ±3.7	0.04
TH	6.1 ± 3.4	3.9 ± 2.9	0.001
tvBMD (tibia)	5.3 ± 5.4	3.4 ± 1.9	0.01
tvBMD (radius)	2.6 ± 4.4	1.0 ± 4.5	0.06
C vBMD (tibia)	2.2 ±1.8	1.6 ± 1.5	0.13
C vBMD (radius)	1.0 ± 2.2	0.3 ± 1.5	0.047
Trab vBMD (tibia)	1.7 ± 2	1.2 ±2.2	0.17
Trab vBMD (radius)	2.2 ±4.0	1.2 ± 4.2	0.14

1145

Prevalence and risk of vertebral fractures in primary hyperparathyroidism: A nested case-control study Henriette Ejlsmark-Svensson*[1,2], Lise Sofie Bislev[1,2], Siv Lajlev[2], Torben Harsløf[2], Lars Rolighed[3], Tanja Sikjær[2], Lars Rejnmark[1,2]. [1]Department of Clinical Medicine, Aarhus University, Denmark, [2]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Denmark, [3]Department of Otorhinolaryngology, Head and Neck Surgery, Aarhus University Hospital, Denmark

IntroductionPrevalence of vertebral fractures (VFx) in patients with primary hyperparathyroidism (PHPT) remains uncertain. The presence of VFx is of importance to choice of treatment. International guidelines recommends parathyroidectomy in patients with PHPT and osteoporosis including the presence of VFx. We aimed to estimate the prevalence of VFx, investigate potential risk factors associated with VFx and whether bone mineral density (BMD) differs between PHPT- and osteoporotic-patients with VFx. MethodsThrough the Danish National Patient Register, we identified patients diagnosed with PHPT between 2005-2015. The diagnosis was verified by retrieving biochemistry data. Patients with ionized-calcium levels above and PTH levels in upper third or above upper limit of the reference range were included (averages of two measurements). X-ray reports of the thoracolumbar spine were reviewed by two investigators. Osteoporotic patients with VFx were identified from our outpatient clinic and matched on age and sex with PHPT patients with VFx. ResultsWe identified 792 PHPT patients among whom spine X-ray was available from 588 patients. VFx were present in 122 (21%) patients and were equally frequent among sex (77% females). Fractured patients were older (70 [IQR: 62-77] yrs. vs 63 [55-71] yrs.) and had lower heights (163 [158-169] cm vs 166 [160-172] cm) compared to non-fractured patients (pall <0.02). After stratification by age-groups, the prevalence of VFx differed significantly between sexes (p<0.01). Ionized-calcium and PTH did not differ between groups. BMD at total hip and forearm were lower in fractured compared to non-fractured patients (pall <0.03) after adjusting for age, sex and BMI. Compared with osteoporotic patients with VFx (N=108), BMD at the lumbar spine was higher in PHPT patients with VFx (N=108) (p<0.01). This did not change by excluding patients with lumbar VFx (p<0.01). ConclusionThe severity of PHPT assessed by biochemistry does not seems to be associated with risk of VFx and the relatively high prevalence of VFx supports a proactive screening in all patients diagnosed with PHPT. Compared with osteoporosis; VFx seems to occur at a higher BMD in PHPT.

*Disclosures: **Henriette Ejlsmark-Svensson, None***

Prevalence and Risk of Vertebral Fractures in Primary Hyperparathyroidism: A Nested Case-Control Study

Henriette Ejlsmark-Svensson,[1] Lise Sofie Bislev,[1] Siv Lajlev,[1] Torben Harsløf,[1] Lars Rolighed,[2] Tanja Sikjaer,[1] and Lars Rejnmark[1]

Table 1. Characteristics of All Patients With Primary Hyperparathyroidism and Stratified by Presence of Vertebral Fractures (No. of Subjects [%] or Median With Interquartile [25–75%] Range)

	All $n = 588$	VFx $n = 122$	No VFx $n = 466$	p Value[a]
Sex				
Male, *n* (%)	135 (23)	29 (21.5)	106 (78.5)	0.81
Female, *n* (%)	453 (77)	93 (20.5)	360 (79.5)	
Age (years)	64 (56–73)	70 (62–77)	63 (55–71)	<0.01
Height (cm)	165 (160–171)[b]	163 (158–169)	166 (160–172)	0.02
Weight (kg)	74 (63–86)[b]	74 (61–82)	74 (64–87)	0.10
BMI (kg/height^2)	26 (24–30)[b]	26 (23–30)	26 (24–31)	0.60
Biochemistry				
Parathyroid hormone (pmol/L)	10.9 (8.5–14.4)	11.4 (8.7–14.7)	10.7 (8.4–14.3)	0.30
Ionized calcium (mmol/L)	1.43 (1.38–1.50)	1.41 (1.37–1.50)	1.43 (1.39–1.50)	0.20
Total calcium (mmol/L)	2.69 (2.60–2.79)	2.68 (2.60–2.80)	2.69 (2.61–2.79)	0.90
eGFR (mL/min)	87 (72–103)	79 (67–100)	88 (74–103)	<0.01
Phosphate (mmol/L)	0.85 (0.74–0.96)[c]	0.86 (0.73–0.98)	0.85 (0.74–0.96)	0.90
Alkaline phosphatase (U/L)	81 (66–104)[d]	76 (63–99)	82 (68–105)	0.03
25-OHD (nmol/L)	68 (53–87)[e]	73 (57–98)	67 (52–82)	<0.05
$1.25(OH)_2D$ (pmol/L)	130 (97–172)[f]	133 (97–169)	130 (97–176)	0.90
Urine calcium (mmol/d)	7.5 (4.7–10.6)[g]	7.4 (4.9–10.5)	7.6 (4.9–10.5)	0.40

Prevalence of vertebral fractures stratified by age groups in males and females

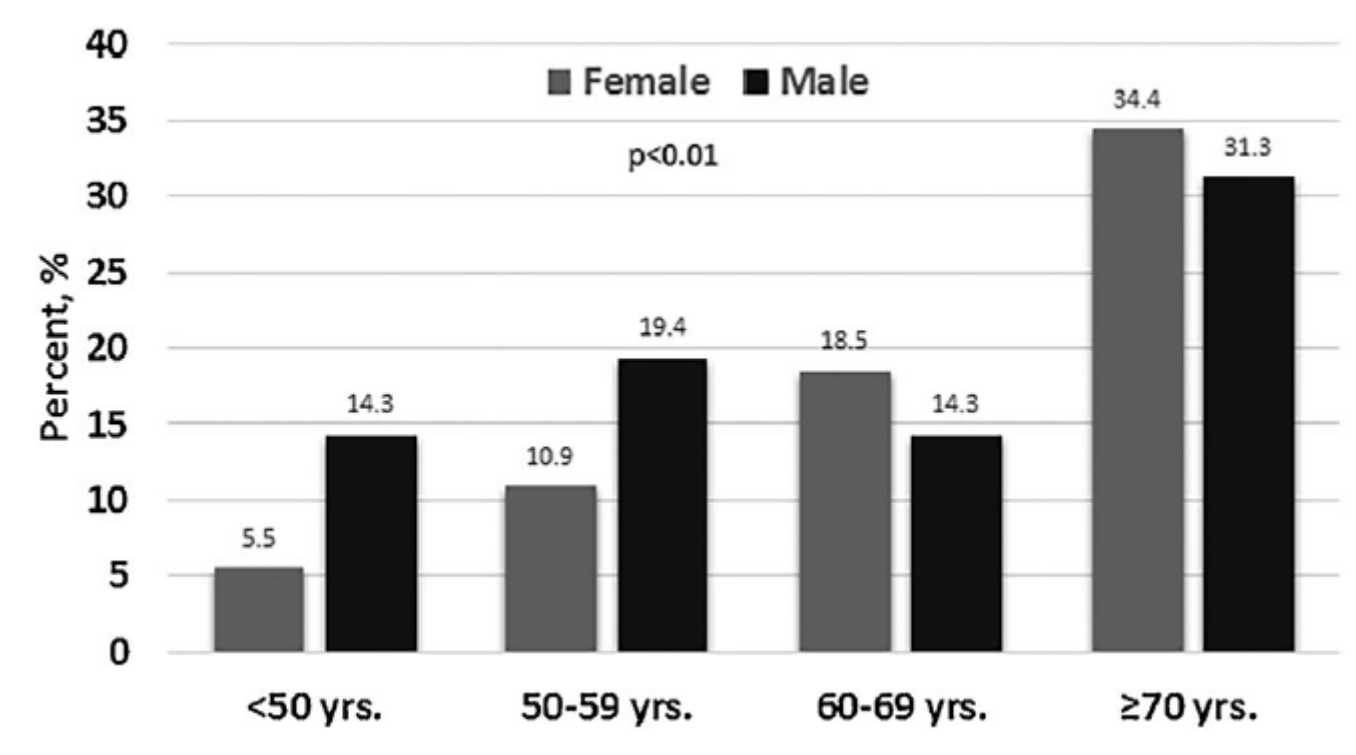


Table 2. Bone Mineral Density in All Patients With Primary Hyperparathyroidism and Stratified by Presence of Vertebral Fractures (Median With Interquartile [25–75%] Range)

	All $n = 543$	VFx $n = 110$	No VFx $n = 433$	p Value[a]	Adjusted p value[a]
Bone mineral density					
Lumbar spine (g/cm^2)	0.906 (0.773, 1.042)	0.880 (0.843, 0.917)[b]	0.918 (0.902, 0.935)[b]	<0.05	0.50[c]
T-score	−1.3 (−2.5, −0.05)	−1.8 (−1.9, −1.2)	−1.2 (−1.3, −1.0)	<0.02	0.30[d]
*T*otal hip (g/cm^2)	0.793 (0.690, 0.925)	0.742 (0.712, 0.772)[b]	0.827 (0.811, 0.842)[b]	<0.01	<0.01[c]
T-score	−1.2 (−2.1, −0.1)	−1.8 (−1.9, −1.4)	−1.0 (−1.1, −0.8)	<0.01	0.02[d]
Femoral neck (g/cm^2)	0.670 (0.582, 0.761)	0.627 (0.601, 0.652)[b]	0.687 (0.674, 0.700)[b]	<0.01	0.06[c]
T-score	−1.6 (−2.4, −0.8)	−2.1 (−2.2, −1.8)	−1.5 (−1.6, −1.3)	<0.01	0.03[d]
Forearm, total (g/cm^2)	0.463 (0.401, 0.526)[e]	0.429 (0.409, 0.450)[b]	0.471 (0.462, 0.480)[b]	<0.01	0.03[c]
Distal 1/3 forearm (g/cm^2)	0.594 (0.522, 0.680)[e]	0.557 (0.533, 0.58)[b]	0.605 (0.593, 0.616)[b]	<0.01	<0.05[c]

The severity of PHPT assessed by biochemistry does not seem to be associated with risk of VFx. Compared with osteoporosis, VFx seems to occur at a higher BMD in PHPT

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Incidence of Malignancies in Fibrous Dysplasia: Data from a National Pathology Cohort Marlous Rotman*, Neveen Hamdy, Bas Majoor, Michiel Van De Sande, Judith Bovee, Sander Dijkstra, Olaf Dekkers, Natasha Appelman-Dijkstra. LUMC, Netherlands

Fibrous dysplasia(FD) is reported to be associated with increased risk for breast and thyroid cancer and for the pre-malignant intraductal papillary mucinous neoplasm (IPMN), possibly due to extra-skeletal tissue distribution of GNAS-mutations. Data on further associations of FD with malignant tumors are scarce. Since these associations may have significant clinical implications, we performed a cohort study on tumor occurrence in FD.Pathology reports from patients with confirmed FD were retrieved from the Dutch National pathology registry (PALGA). Incidence rates for malignant tumors were estimated and compared between FD patients and the general Dutch population by calculating standardized morbidity ratios (SMR). In this study, SMRs were calculated for all histologically confirmed FD/GNAS-associated and bone tumors. We also studied the FD associated risk for the three most common malignancies in the Netherlands, e.g. prostate, colorectal and skin cancer; our data on breast cancer have been reported previously.Of the 1146 PALGA FD patients, 177 (M/F; 79/98) also had histological evidence for a malignant tumor. Mean age at FD diagnosis was 47.0 years (1-86yr) and mean age at diagnosis of malignancy was 49.7 years (2-92yr). 207 malignant tumors were documented. Among known GNAS-related and bone tumors, SMR was increased for thyroid cancer (3.71[95%CI 1.13-7.76]) and for osteosarcoma (26.31[95%CI 6.58-59.20]). For the three most prevalent malignancies in The Netherlands, SMRs were increased for prostate cancer (3.08[95%CI 1.82-4.63]) and melanoma (1.99[95%CI 1.05-2.94]), but not for colorectal cancer.Our data confirm that patients with FD have an increased risk for thyroid cancer and osteosarcoma. We also report for the first time an increased risk for a number of other malignancies in FD such as melanoma and prostate cancer, which both have not priviously been associated with GNAS-mutations, but no increased risk for pancreatic cancer was found. Our findings raise awareness for the risk of malignancy in FD, although caution should be exerted in the interpretation of these data, as true incidence rates of malignancy might have been underestimated by the inclusion in this study of only patients with histologically-confirmed FD, and the specific role of GNAS mutations in the pathophysiology of FD-related tumors is as yet to be unraveled.

Disclosures: Marlous Rotman, None

PALGA FD patients

- 1146 pts
- 177 (M/F; 79/98) evidence of malignant tumor
  - Thyroid Cancer: 3.71[95%CI 1.13-7.76]
  - Osteosarcoma : 26.31[95%CI 6.58-59.20]
  - Prostate cancer: 3.08[95%CI 1.82-4.63]
  - Melanoma: 1.99[95%CI 1.05-2.94]

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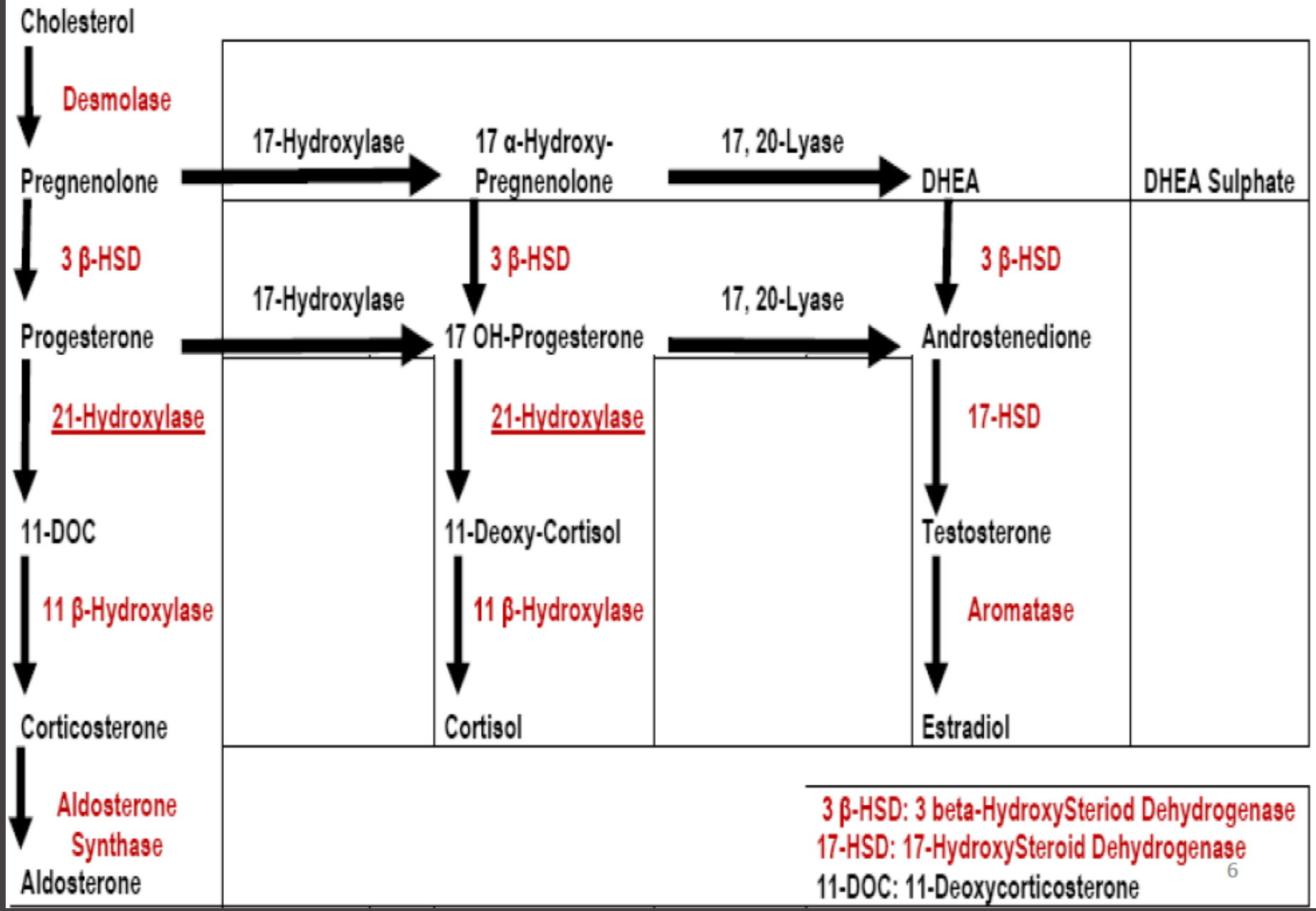
Towards a physiologically-based definition of hypogonadism: Dose-response relationships between testosterone and bone density in older men Elaine Yu*, Benjamin Leder, Hang Lee, Laura Krivicich, Emily Gentile, Sarah Hirsch, Karin Darakananda, David Lin, Joel Finkelstein. Massachusetts General Hospital, United States

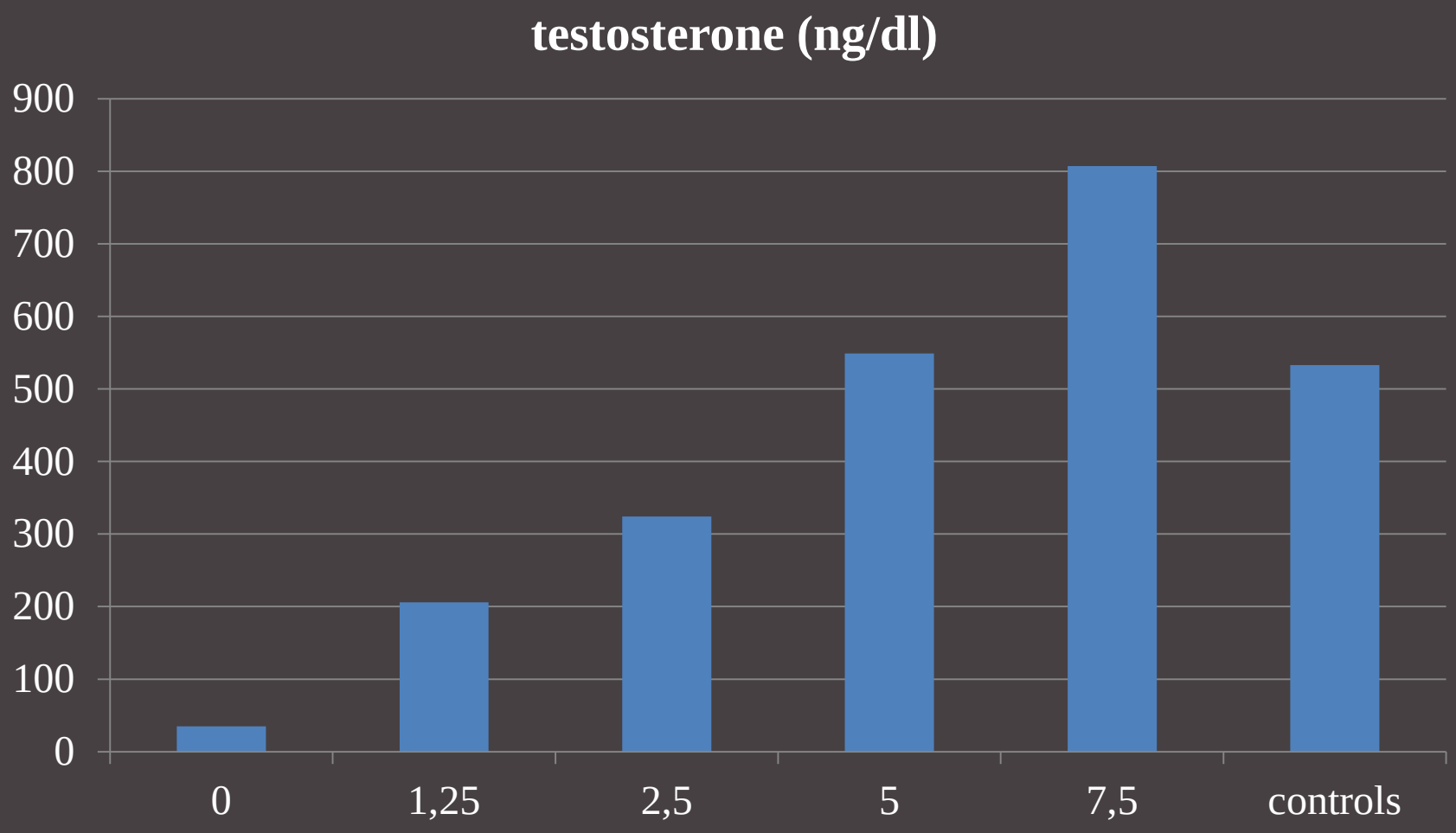
Introduction: Testosterone (T) replacement in older men is controversial, partly due to a lack of a physiologically-based definition of late-onset hypogonadism. We previously found that T levels above 200 ng/dL prevented increases in bone resorption and decreases in bone mineral density (BMD) in young men. However, it is not clear whether the same physiologic thresholds apply to older men. Thus, we performed a randomized controlled physiologic study in older men to determine the T thresholds that lead to bone loss.Methods: Healthy men aged 50-75 (n=177) were randomized to 1 of 6 groups. Groups 1-5 received goserelin acetate (Zoladex®, AstraZeneca LP, 3.6 mg q4wk) to induce severe hypogonadism, together with 0 (placebo), 1.25, 2.5, 5, or 7.5 g/day of a T gel (AndroGel®, Abbvie) for 16 weeks. Group 6 (Controls) received placebo Zoladex® and placebo Androgel®. BMD of lumbar spine was assessed by DXA (L1-L4) and by QCT (L4). Serum C-telopeptide (CTX) was measured at weeks 0 and 16 to assess bone resorption. The mean percent change from baseline of CTX and spine BMD for the Controls was compared with the mean change for each of the other 5 groups using Dunnett's test for multiple comparisons.Results: Mean age at baseline was 65 ± 4 years. Mean baseline T levels were 490 ± 151 ng/dL in the full cohort, and were similar in each of the 6 groups. Mean (± SD) serum T and E levels measured every 4 weeks were 35 ± 34, 206 ± 116, 324 ± 162, 549 ± 290, and 807 ± 381 ng/dL and 3 ± 2, 11 ± 7, 15 ± 7, 28 ± 13, and 36 ± 18 pg/mL in the 0, 1.25, 2.5, 5, and 7.5 g/day T dose groups, respectively, and 533 ± 142 ng/dL and 28 ± 5 pg/mL in the Controls. Serum CTX increased 103 ± 57% in the 0 g/day T group and 41 ± 30% in the 1.25 g/day T group ($P<0.01$ vs Controls for both), but did not differ significantly from Controls in groups that received 2.5, 5, or 7.5 g/day of T. When assessed by QCT, spine BMD decreased by -6 ± 8%, -5 ± 7%, and -5 ± 8% in groups that received 0, 1.25, or 2.5 g/day of T ($P<0.05$ vs Controls for each of the 3 groups). There were no differences in DXA spine BMD in any group compared with Controls.Conclusions: The strong dose-response relationships between T dose and CTX and BMD in older men suggest that increased bone resorption and bone loss begin when serum T levels fall below 200-300 ng/dL and serum E2 levels fall below 10-15 pg/mL. These data suggest that the relationship between gonadal steroid levels and bone health is similar in older and younger men.

Abstract 1147

- Σκοπός: καθορισμός του επιπέδου τεστοστερόνης που οδηγεί σε οστική απώλεια σε ηλικιωμένους άνδρες.
- Ομάδα μελέτης: 177 άνδρες (50-75 ετών)
- 6 Ομάδες
- Ομάδες 1-5: goserelin acetate (Zoladex, 3.6 mg q4wk) και 0 (placebo), 1.25, 2.5, 5, or 7.5 g/day of a T gel (AndroGel) for 16 weeks
- Ομάδα 6: placebo Zoladex and placebo Androgel
- BMD, QCT (L4), CTX at: 0 and 16 wks

Fig. 1: Flow diagram of pathways for biosynthesis of steroid hormones

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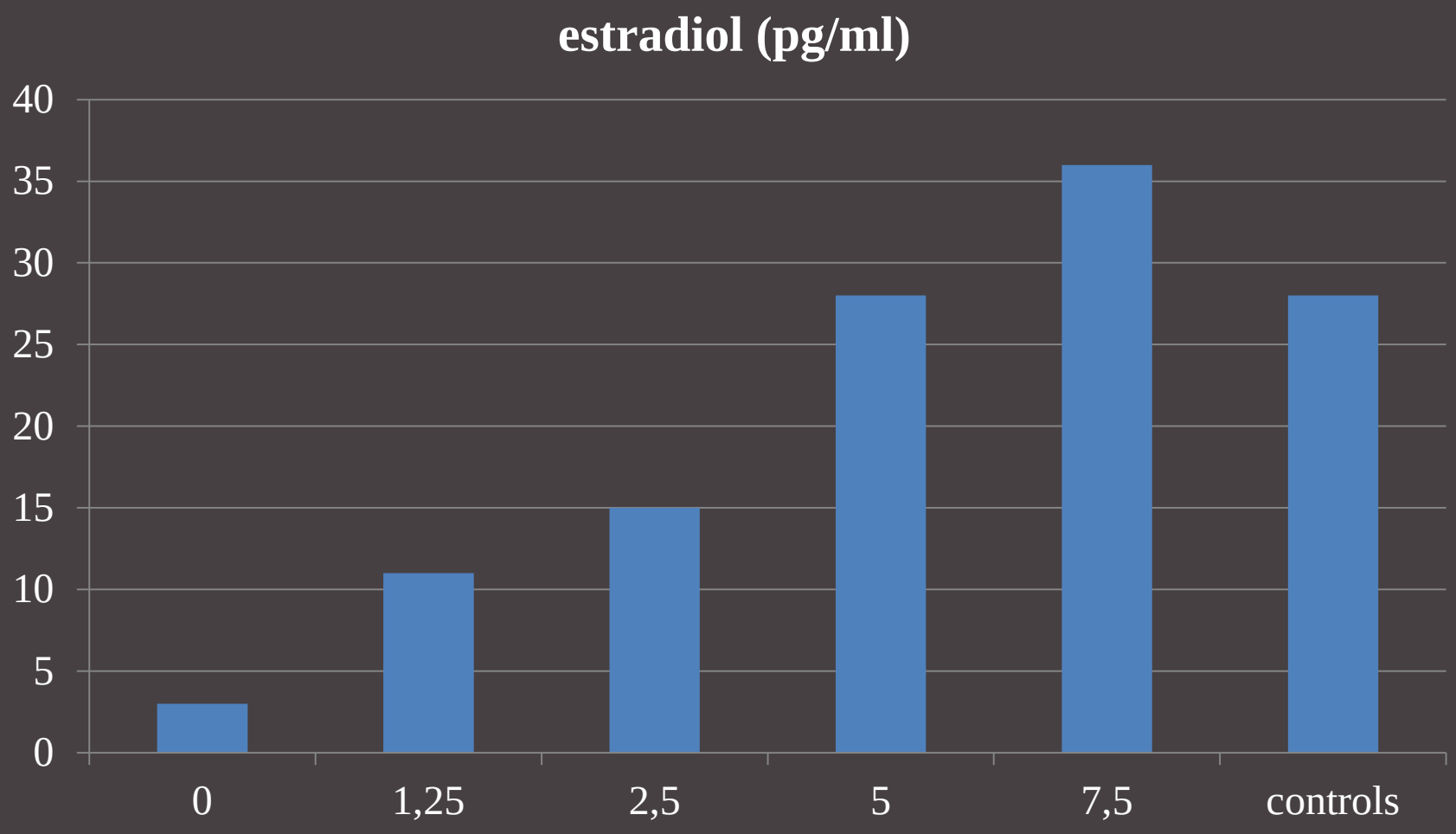
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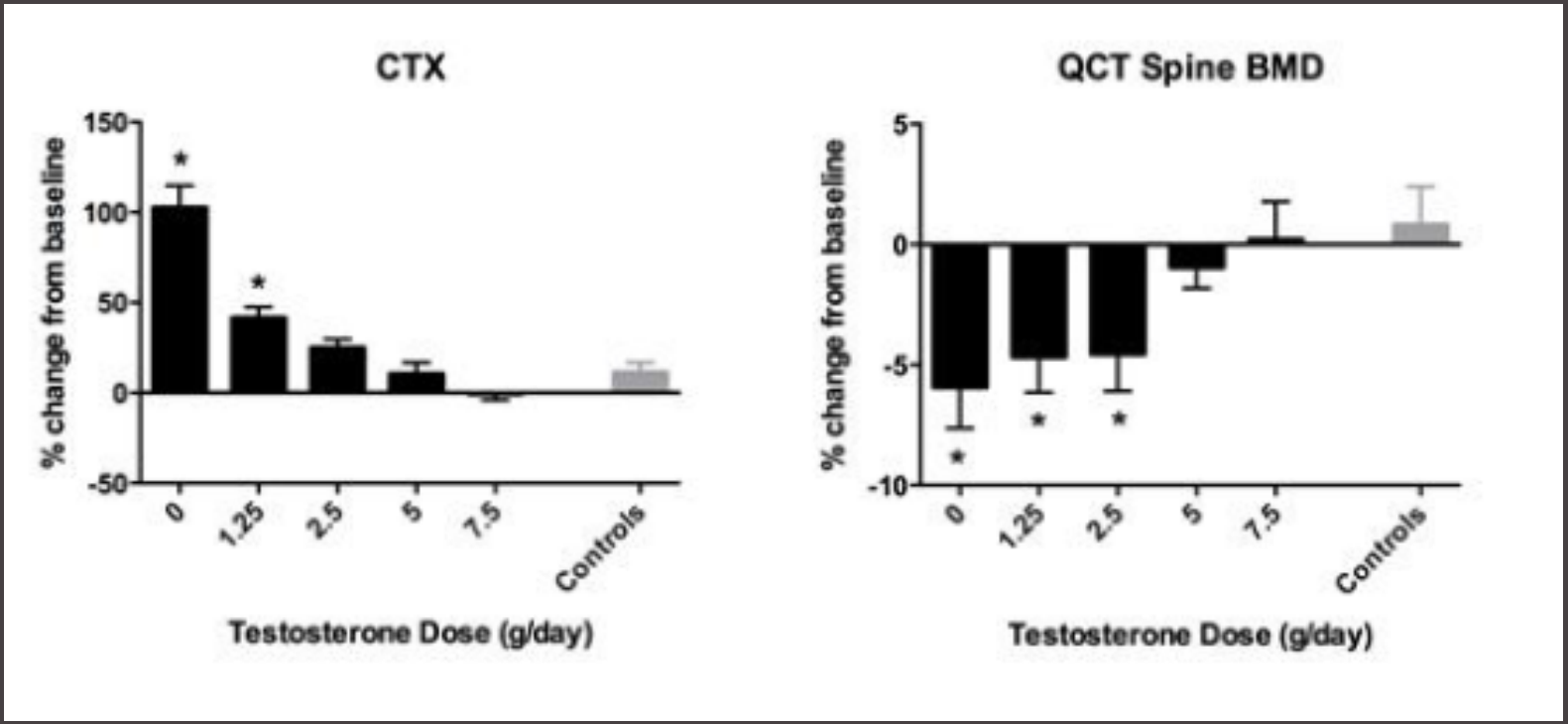

Conclusions: The strong dose-response relationships between T dose and CTX and BMD in older men suggest that increased bone resorption and bone loss begin when serum T levels fall below 200-300 ng/dL and serum E2 levels fall below 10-15 pg/mL. These data suggest that the relationship between gonadal steroid levels and bone health is similar in older and younger men.

Ερωτήσεις ?