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FARMACI ANABOLICI E DOLORE DA OSTEOPOROSI

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Disclosure

Data included in this presentation are from scientific peer-reviewed publications
and from the speaker's own clinical practice

All material is intended for medical education purposes only

Received grant or fee for lecture or consultant in the last 2 years: ELI Lilly,UCB AMGEN, Amryt

What is Pain?

- "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"

(International Association for the Study of Pain, 1979)

- As a complex phenomenon derived from sensory stimuli
- Interpreted by the individual, there are no biological markers for pain
- Evidenced by self-reporting

"Pain Management" Connie Steigmeyer RN, MSN
Health Care Excel Medicare Quality Improvement Organization

Why Focus on Pain?

- Symptom most expected and most feared by patients
- Unrelieved pain can have enormous physiological and psychological effects on the resident and caregivers
- Negatively affects **quality of life** by impairing daily functions, social relationships, sleep, and self worth

"Pain Management“ Connie Steigmeyer RN, MSN
Health Care Excel Medicare Quality Improvement Organization

L’angelo del Dolore

W.W. Story 1894 Cimitero Acattolico di Roma

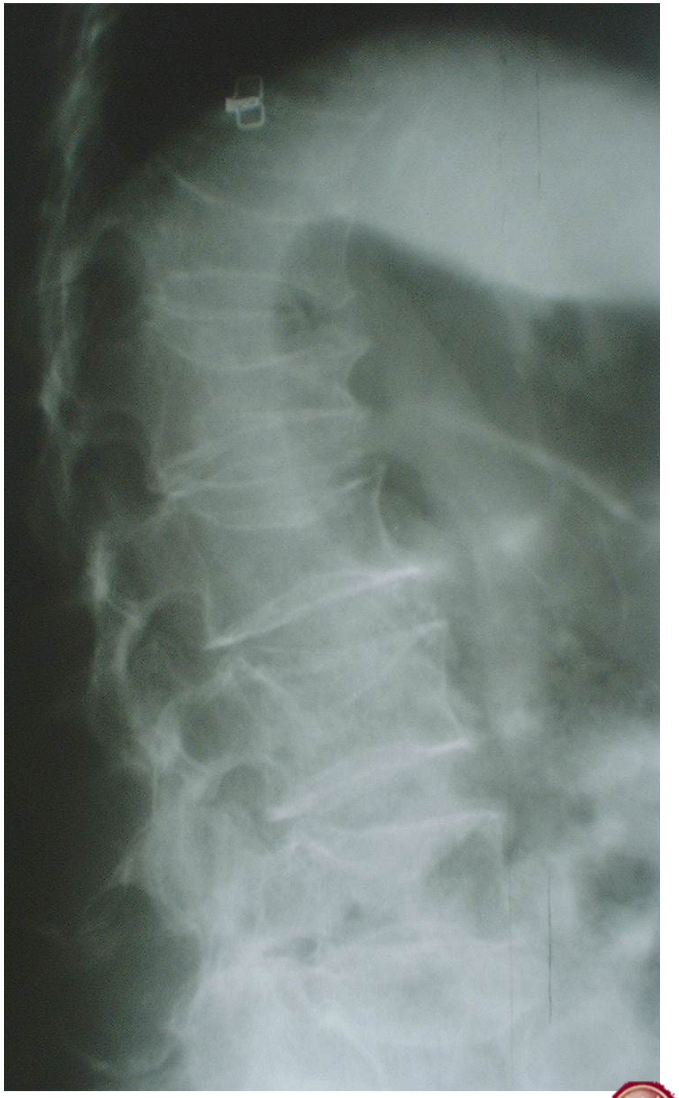
Osteoporosis: Vertebral Fractures

Vertebral fractures are the most common type of fracture occuring in patients with osteoporosis.

Nevitt MC et al,Ann Intern Med 1998; 1\28: 793-800

With fracture of the spine, pain results from collapse of the vertebrae and is typically acute, although chronic pain can also occur (possibly due to changes in the architecture of the vertebrae and supporting structures, such as muscle and ligaments).

Krane SM et al, Metabolic Bone Disease 1998: 2247-59



Classificazione del Dolore in base alla durata

1. Transitorio: causato dall'attivazione dei nocicettori, corpuscoli responsabili della trasmissione degli stimoli dolorosi, senza provocare danno tissutale. Tutto scompare con la cessazione dello stimolo.

2. Acuto: è un dolore nocicettivo di breve durata in cui solitamente il rapporto causa/effetto è evidente; nel dolore acuto, per effetto di una causa esterna o interna, si ha una fisiologica attivazione dei nocicettori. In genere si ha un danno tissutale e il dolore scompare con la riparazione del danno.

3. Persistente: la permanenza dello stimolo nocicettivo o della nocicezione rendono il dolore "persistente".

4. Cronico Si definisce tale un dolore che persiste da più di sei mesi. È un dolore associato a profonde modificazioni della personalità e dello stile di vita del paziente che restano persistenti indipendentemente dall'azione dei nocicettori.

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Clinical of Vertebral Fracture

Social isolation, loss of self-esteem and depression

Back pain

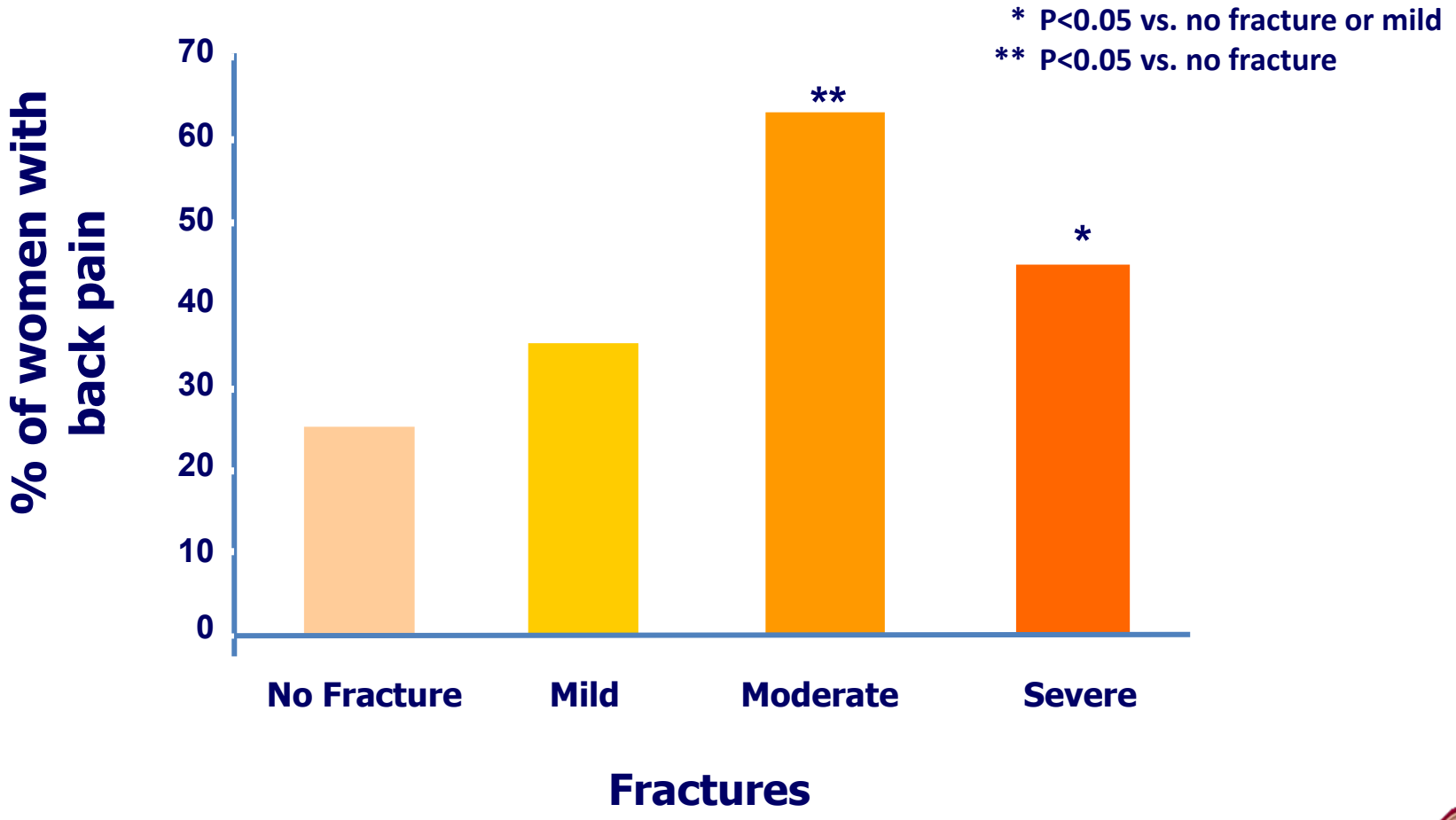
Kyphosis
Height loss

Altered posture

Decreased pulmonary function and gastroesophageal reflux

Fracture Prevention Trial

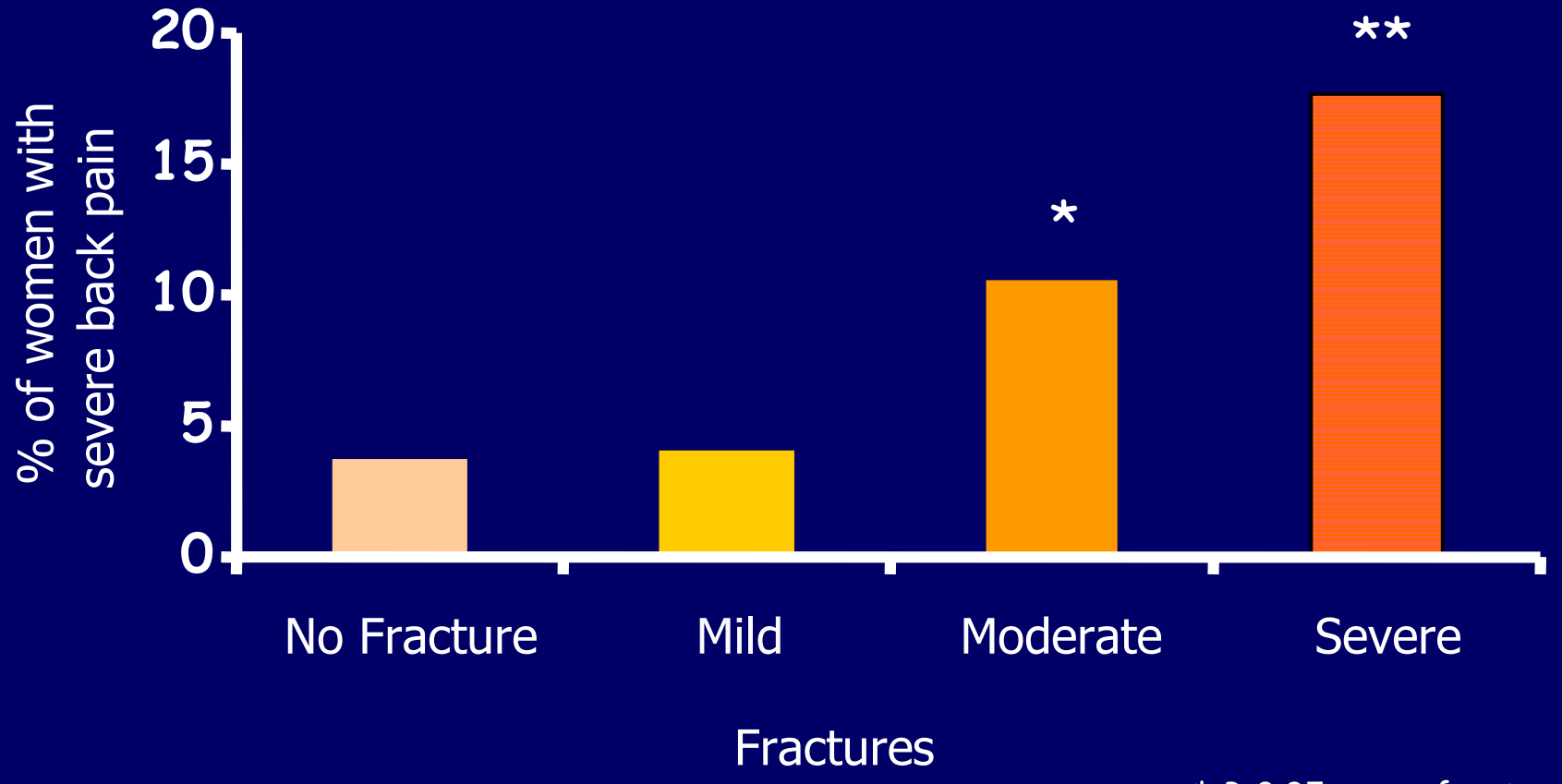
Incidence of Back Pain Related to Vertebral Fracture Grade



Genant HK, Arthritis Rheum 2000; 43 (9, Supplement):S383

Fracture Prevention Trial

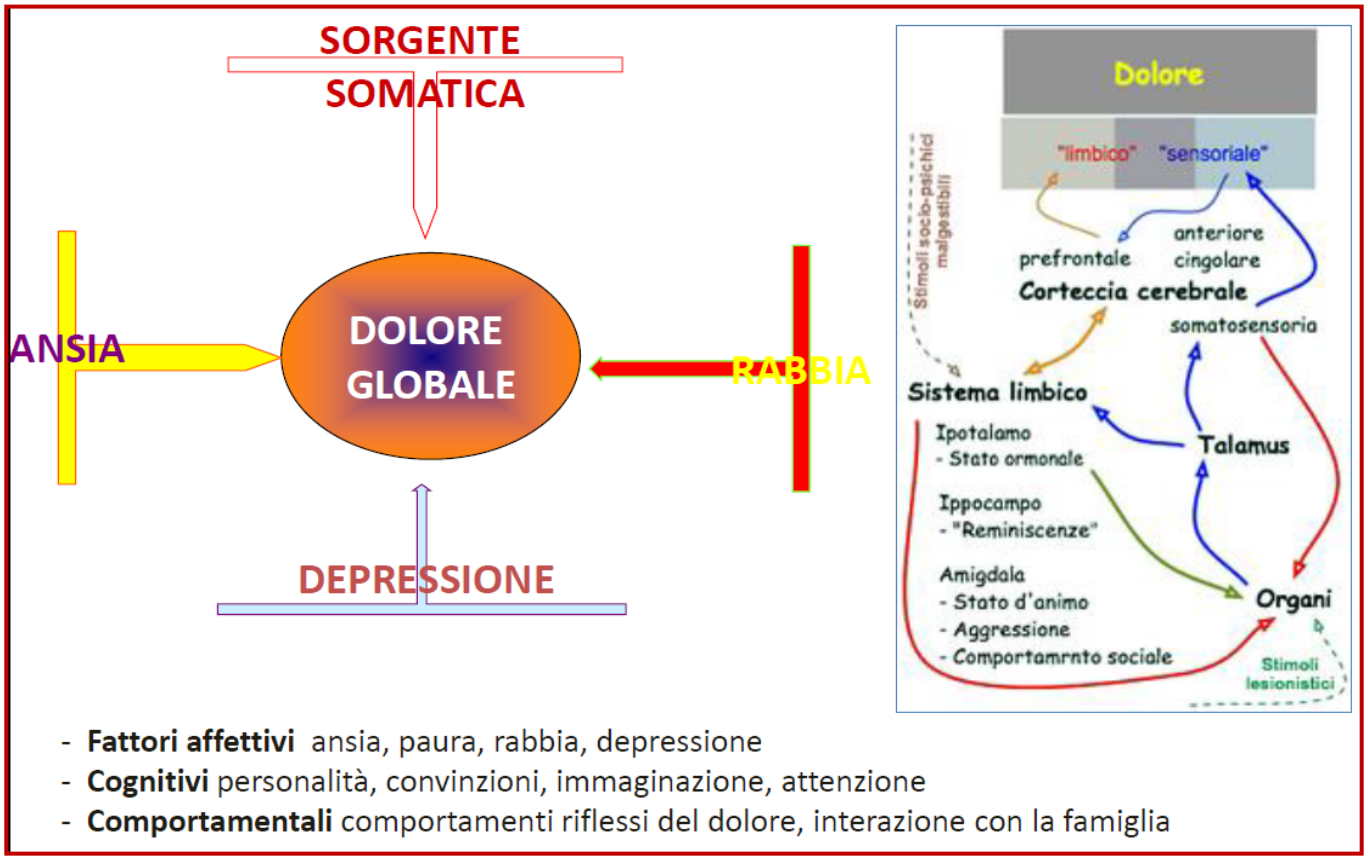
Incidence of Severe Back Pain is related to Vertebral Fracture Grade



* P<0.05 vs. no fracture
** P<0.01 vs. no fracture

t HK, Arthritis Rheum 2000; 43 (9, Supplement):S383

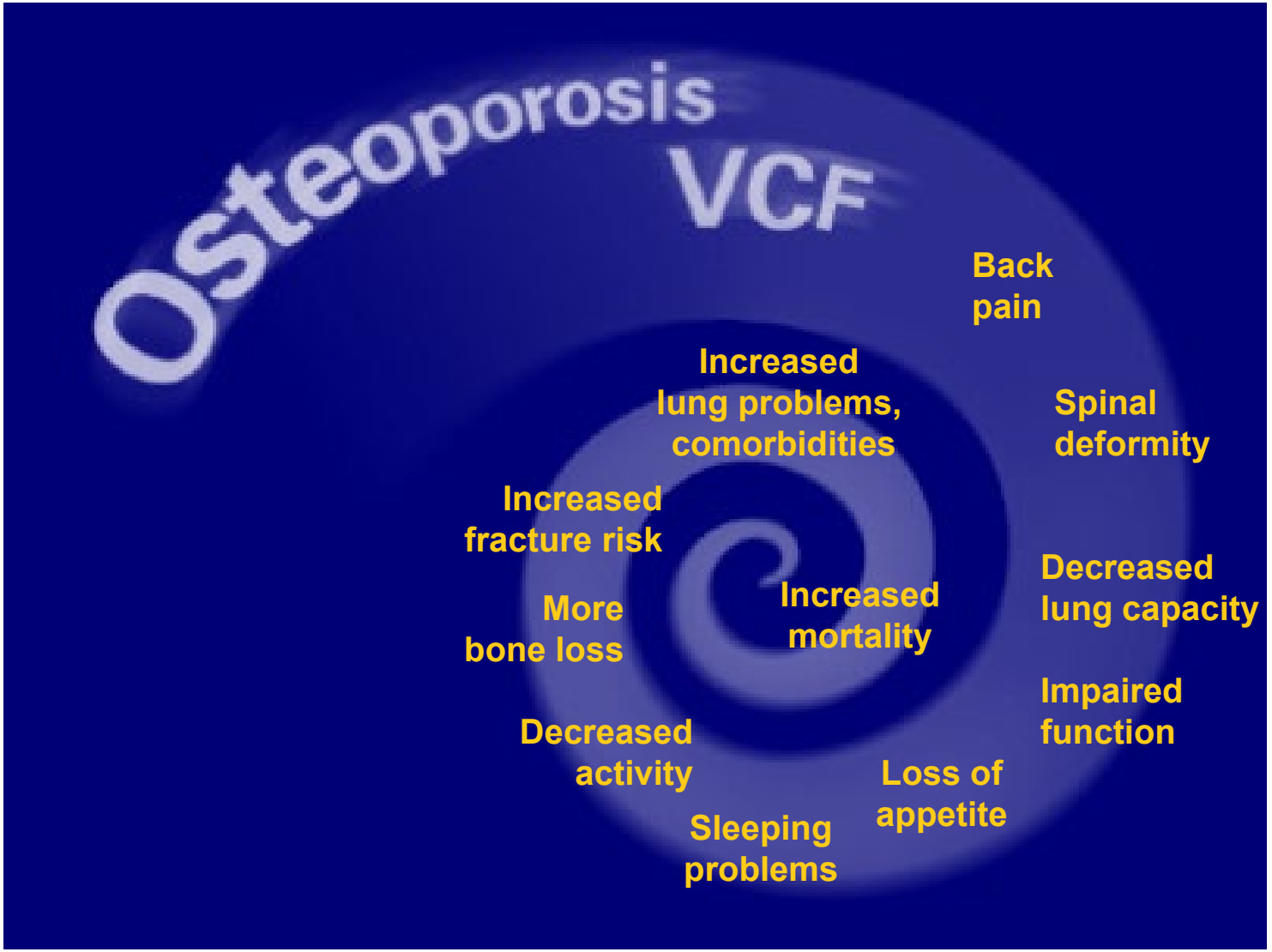
Componenti alla sensazione del dolore



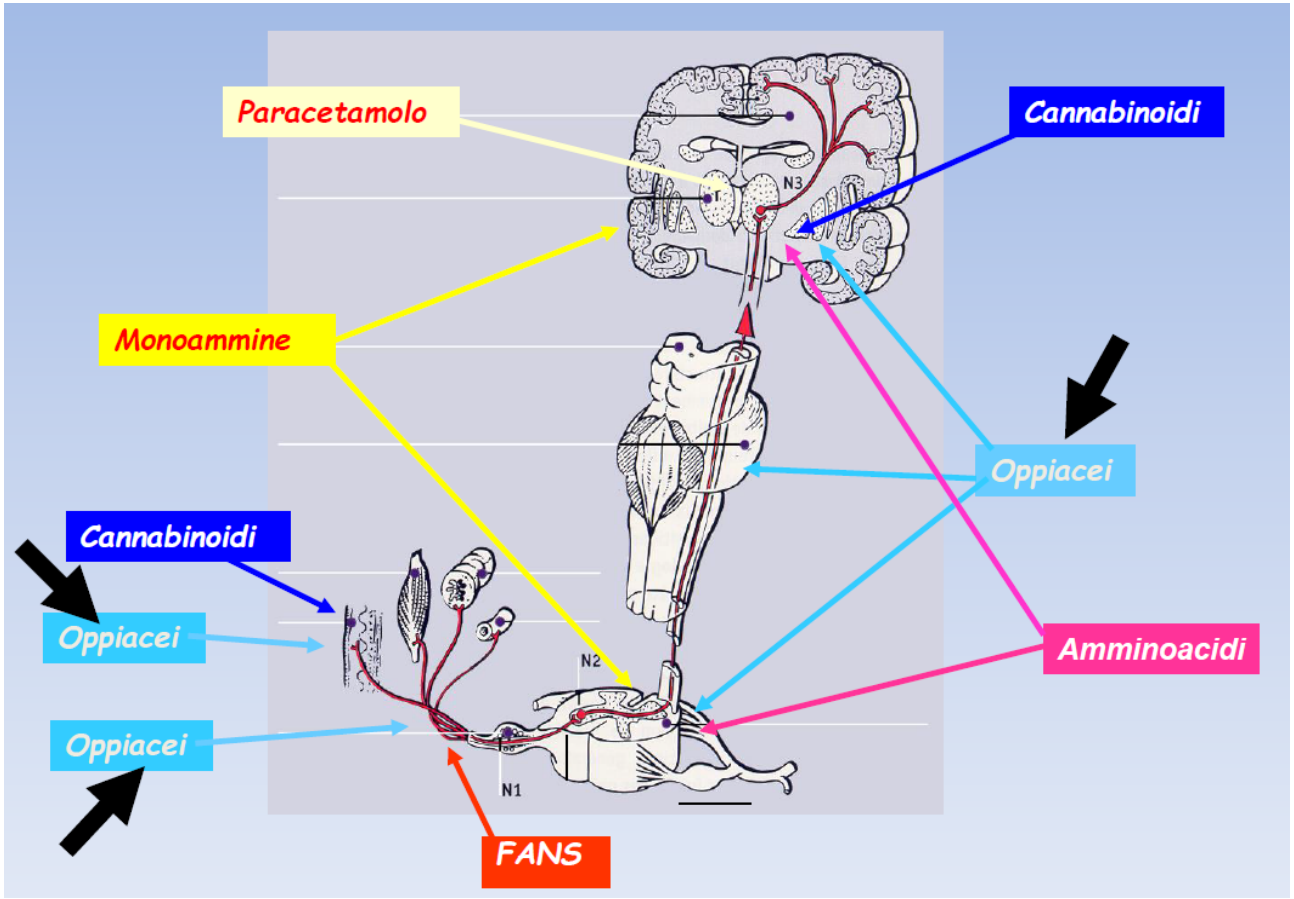
- **Fattori affettivi** ansia, paura, rabbia, depressione
- **Cognitivi** personalità, convinzioni, immaginazione, attenzione
- **Comportamentali** comportamenti riflessi del dolore, interazione con la famiglia

EZIOLOGIA e MECCANISMI DEL DOLORE

A vicious downward spiral of physical, social and psychological consequences



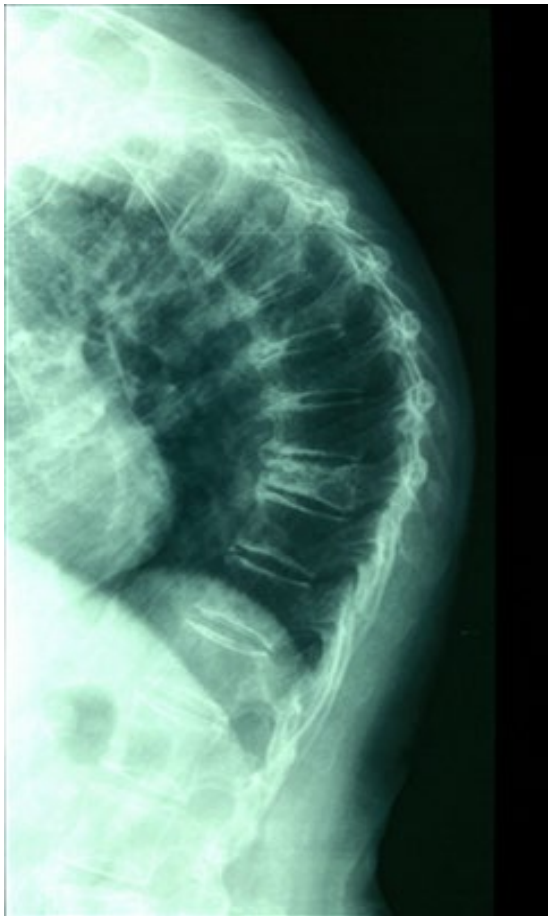
Trattamento del Dolore



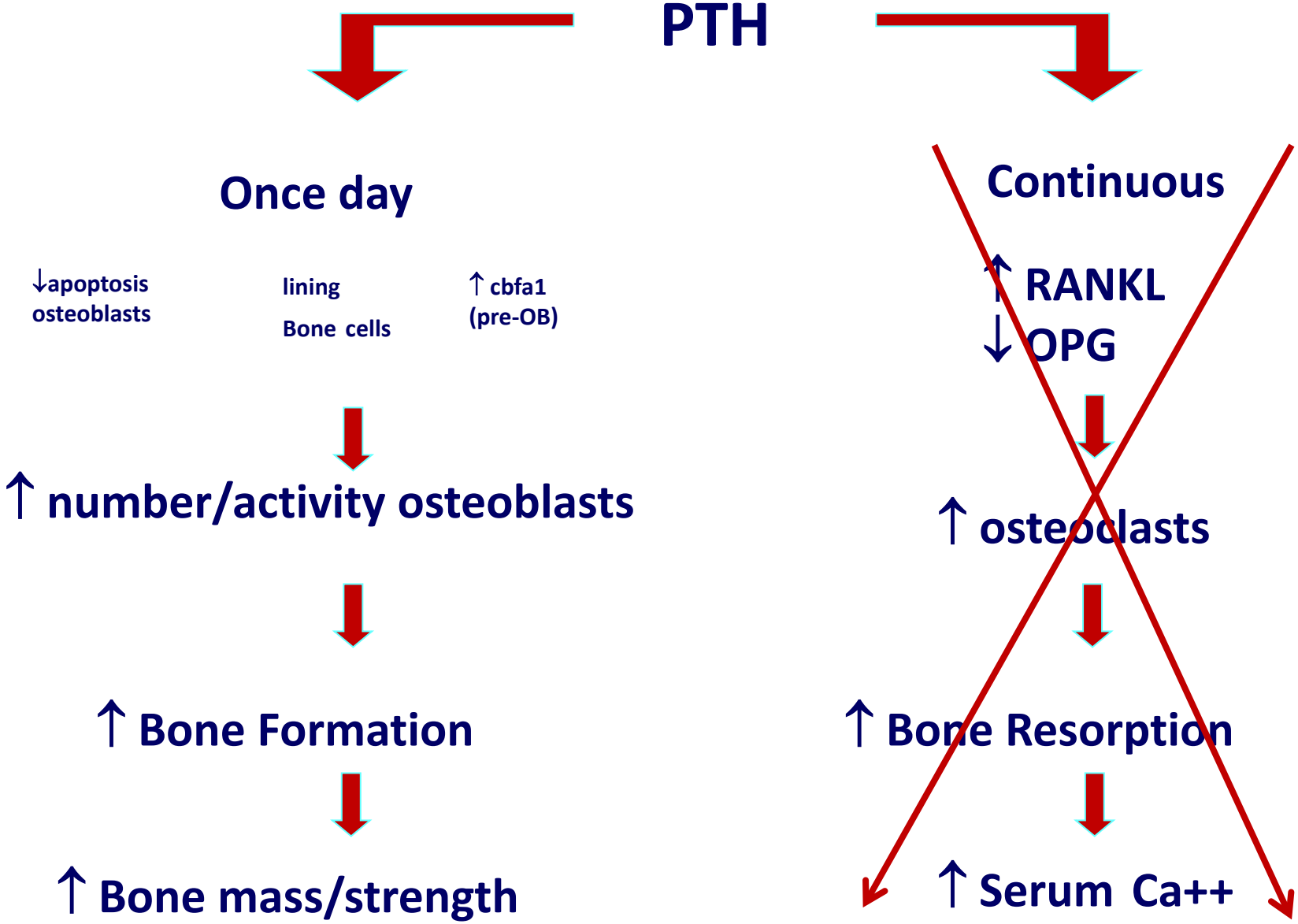
Back Pain and Vertebral Fractures

- The etiology of back pain is multifactorial and may represent muscular pain, instability of the spine, facet arthropathy or degenerative disc disease

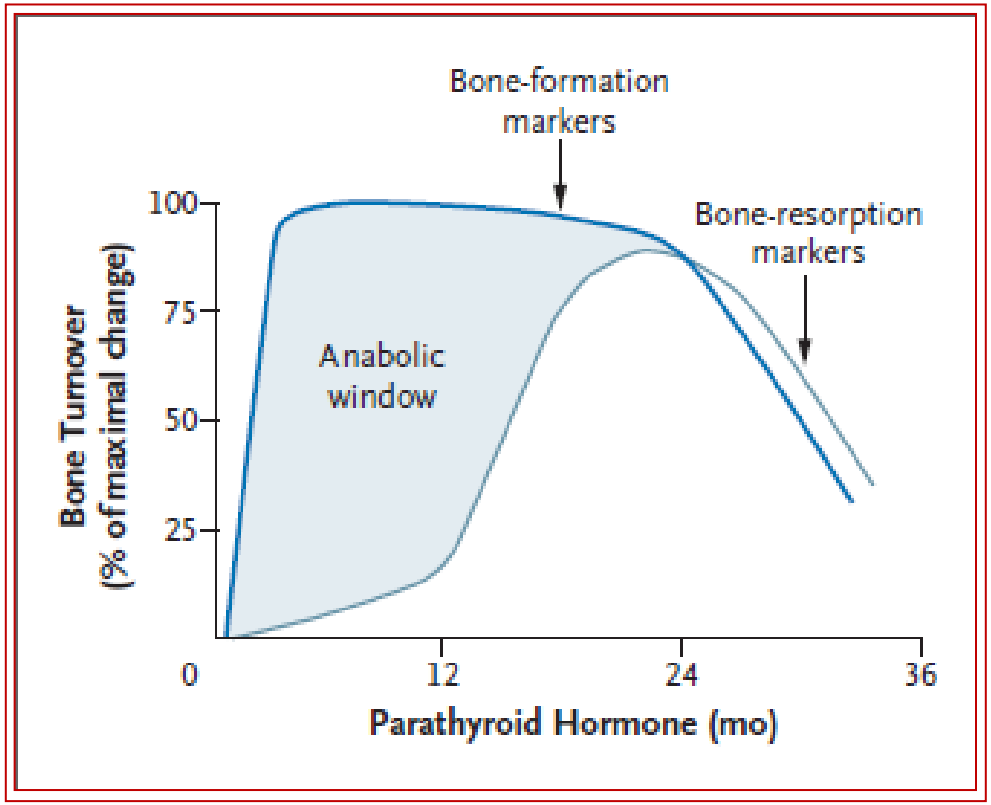
- The severe pain associated with syntomatic vertebral fractures usually persist for several weeks, before gradually improving and alters quality of life of osteoporotic patients



Francis RM et al Q J Med, 2004; 97: 63-74

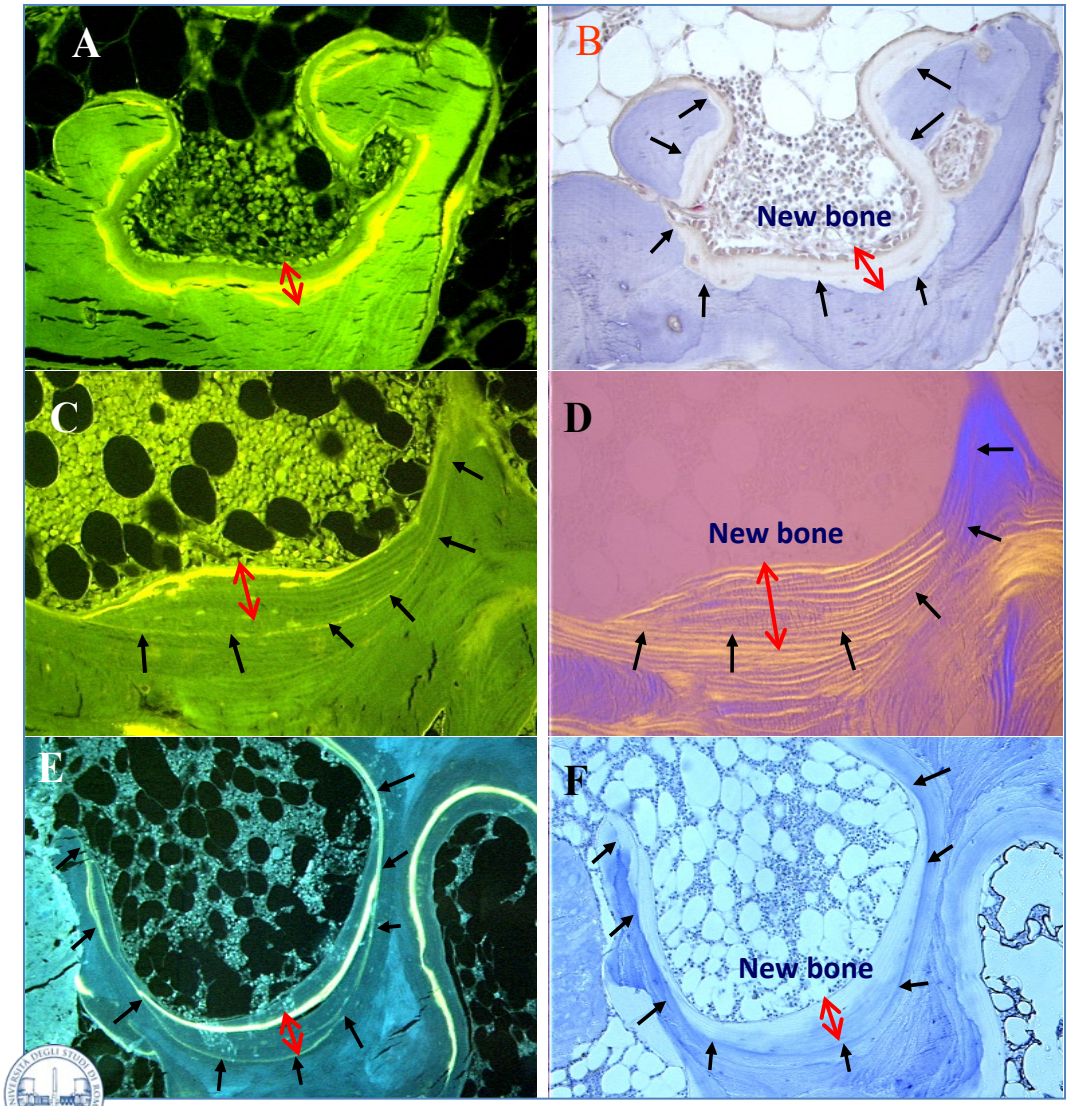


Dobnig H and Turner RT Endocrinology 1995, Ma YL Endocrinology 2001
Jilka J Clin Invest 1999, Hock J Musculoskel Neuron Interact 2001



Brommage, et al. *JCEM* 1999;84:3757-63; Hirano , et al. *CTI* 2000;66:456-60; Jerome, et al. *Bone* 2001 28:150–9; Sato, et al. *Osteoporos Int* 2000;11:871-80; Sato, et al. *JBMR*2004; 9:623-29

Teriparatide induces formation of new bone



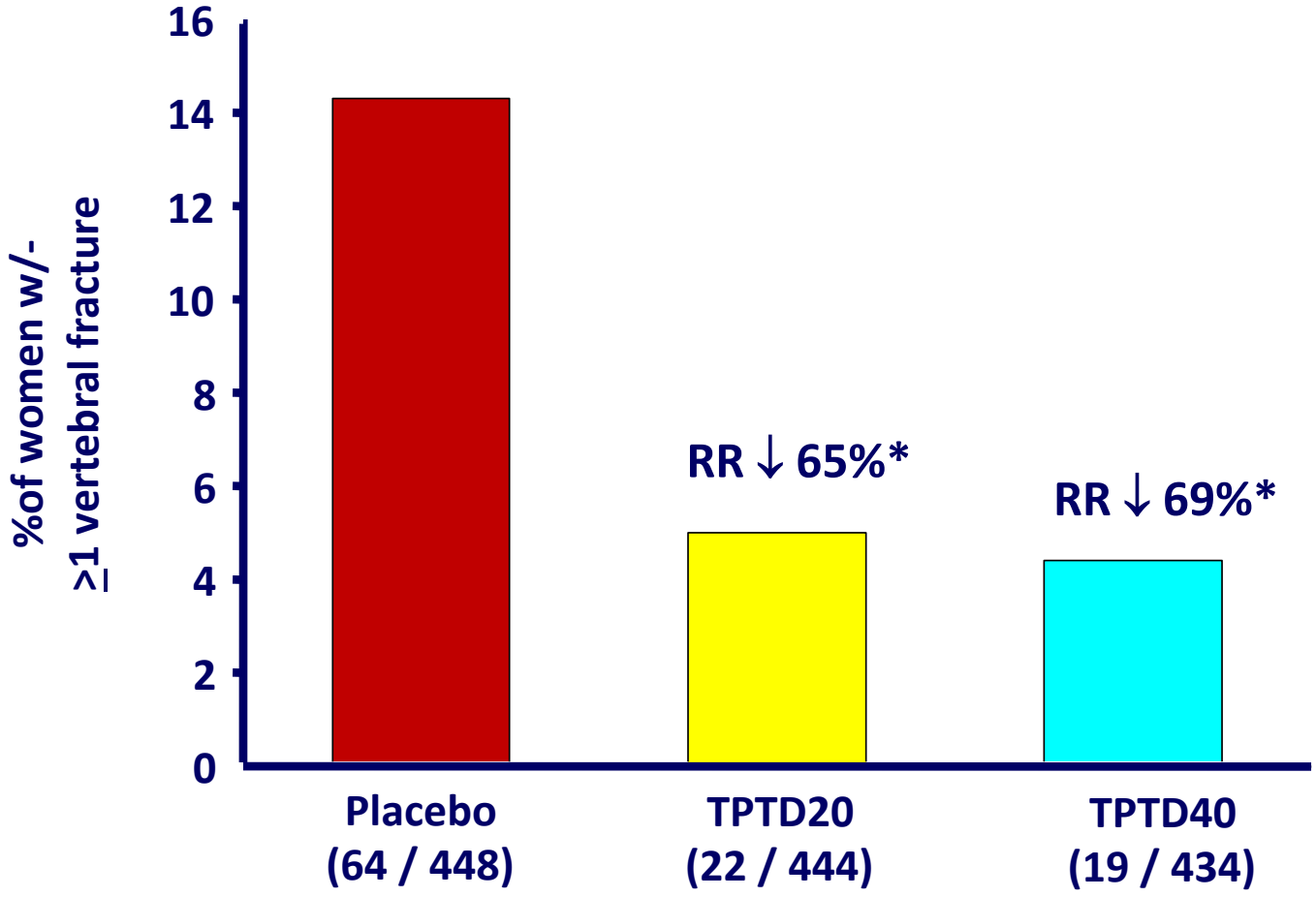
Remodeling osteon

Modeling osteon at quiescent surfaces- New bone formation

Mixed remodeling-modeling osteon Prolonged formation on remodeling osteon

Ma, et al. *J Bone Miner Res* 2006;21:855-64

Fracture Prevention Trial: Effect of Teriparatide & risk of new vertebral fractures



Adapted from Neer et al. N Engl J Med 2001

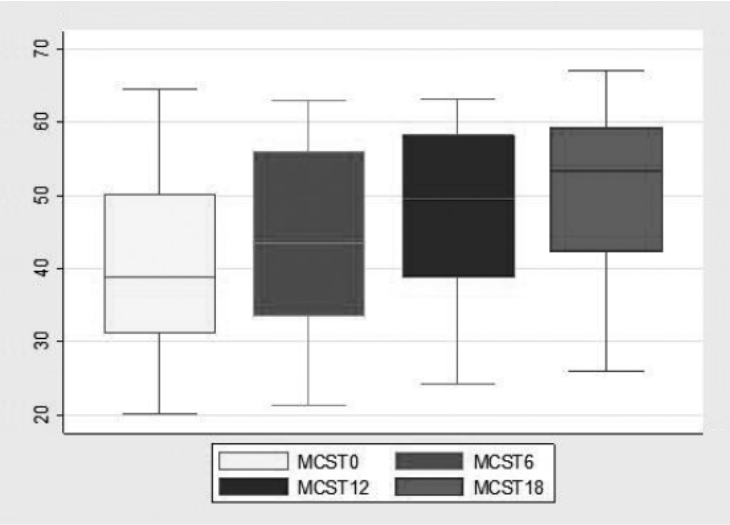
*P <0.001 vs. placebo
RR = rischio relativo vs. placebo

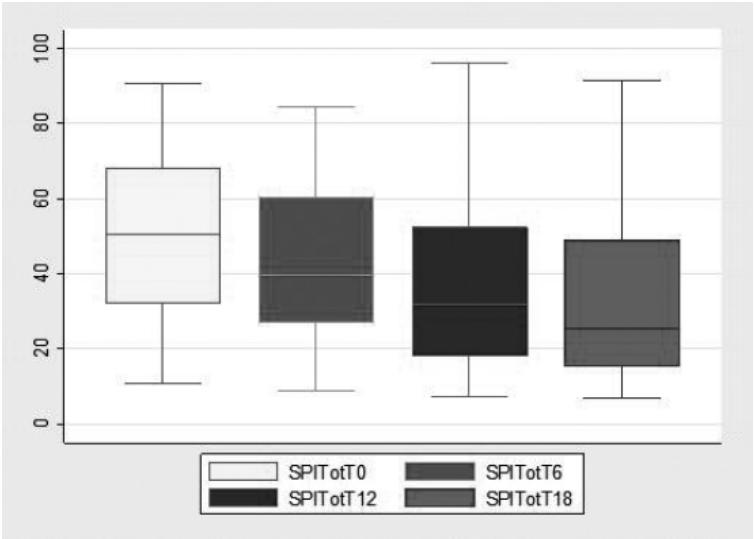
Clinical Cases in Mineral and Bone Metabolism 2012; 9(3): 161-165

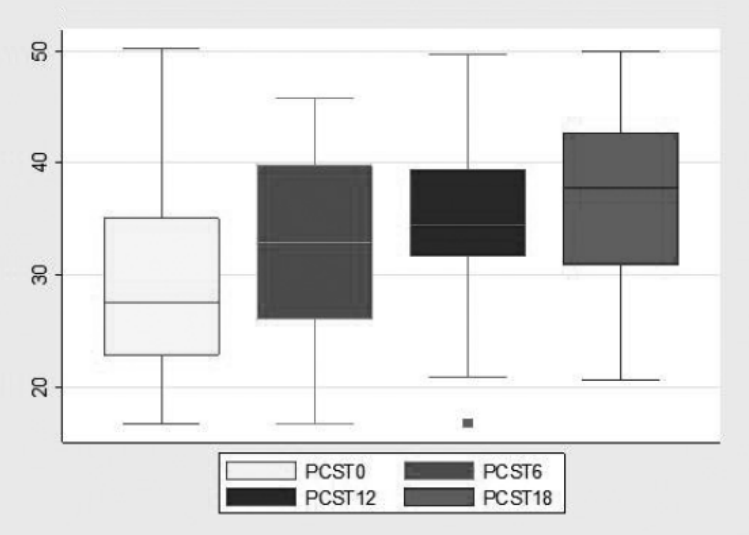
Original article

Effectiveness of teriparatide treatment on back pain-related functional limitations in individuals affected by severe osteoporosis: a prospective pilot study

Giovanni Iolascon[1]
Francesca Gimigliano[2]
Nazzarena Malavolta[3]
Umberto Tarantino[4]
Rachele Fornari[5]
Emanuela Greco[5]
Gioconda Di Pietro[1]
Raffaele Gimigliano[1,6]
Andrea Lenzi[5]
Giuseppina Resmini[7]
Silvia Migliaccio[5,8]







Bone Reports 13 (2020) 100728

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

The efficacy of teriparatide on lumbar spine bone mineral density, vertebral fracture incidence and pain in post-menopausal osteoporotic patients: A systematic review and meta-analysis☆

Shakib Akhter [a,b], Abdul Rehman Qureshi [a], Hussein Ali El-Khechen [a], Anthony Bozzo [a,b], Moin Khan [a,b], Rakesh Patel [d], Mohit Bhandari [a,b,c], Ilyas Aleem [d,*]

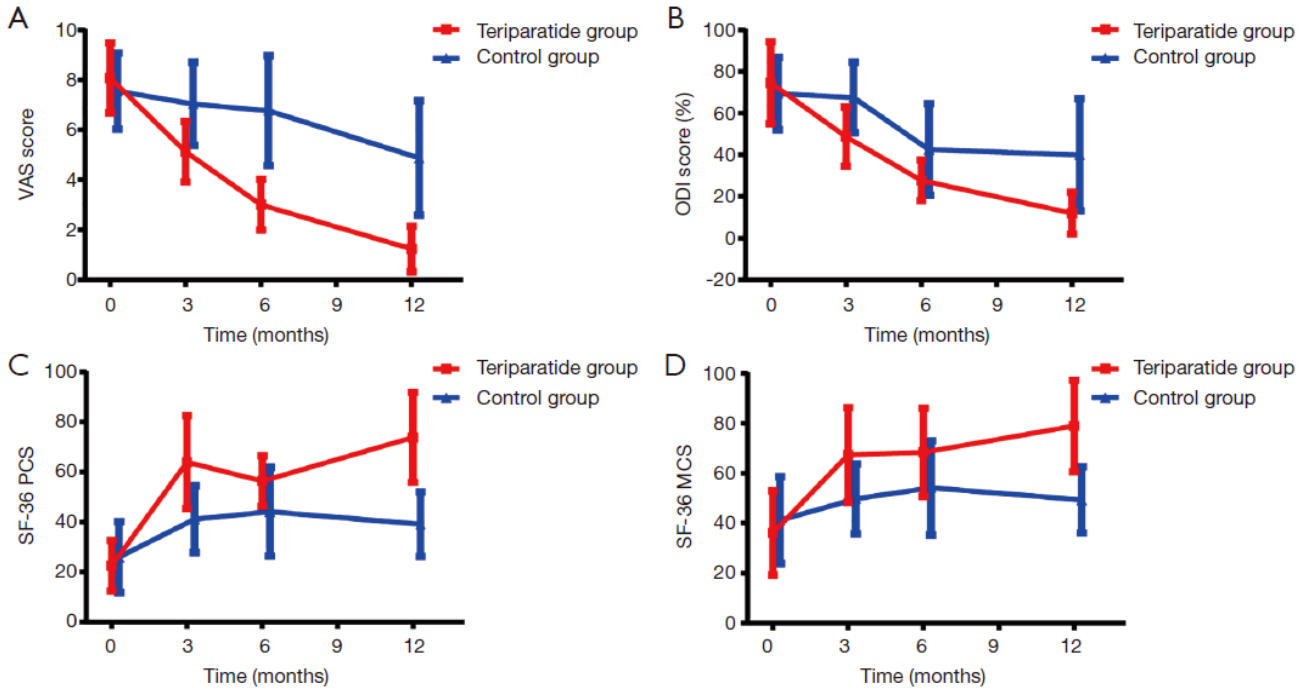
Results: A total of 20 studies (n = 6024) were included in this review, with 2855 patients receiving teriparatide and 3169 patients receiving placebo or control treatment. A teriparatide dose of 20 μg/day increased lumbar spine bone mineral density (BMD) (standardized mean difference (SMD) 0.34 standard deviation (SD) units higher (95% CI 0.19–0.48 SDs higher) in comparison to placebo. Relative to anti-resorptive agents, 20 μg/day of teriparatide had a range from 0.14 SD units to 0.96 SD units higher (95% CI, 0.08 SDs lower to 0.36 SDs higher, CI, 0.33–1.59 SDs higher, respectively). 20 μg/day teriparatide had a significant effect on pain severity to placebo or control (SMD 0.80, 95% CI, 1.16–0.43 SDs lower) and also decreased the incidence of vertebral fractures compared to placebo (relative risk 0.31, 95% CI 0.21 to 0.46). Arthralgia and extremity pain incidence were also calculated; there were 15 and 8 fewer events per 1000 patients with the use of 20 μg/day of teriparatide compared to placebo or control, respectively.

Conclusion: High quality evidence supports the utilization of teriparatide 20 μg/day dose to significantly improve lumbar spine BMD and decrease incidence of vertebral fractures and pain severity relative to all comparators. 40 μg/day dose of teriparatide demonstrated significantly better results with prolonged treatment. This data is valuable for clinicians involved in the care of this growing demographic of patients. Further investigation on the safety and efficacy of teriparatide in higher doses for the long-term treatment of osteoporosis in postmenopausal women should be conducted through high-quality clinical trials.

Ann Palliat Med 2021;10(4):4000-4007 | http://dx.doi.org/10.21037/apm-20-2333

Effect of Teriparatide on pain relief, and quality of life in postmenopausal females with osteoporotic vertebral compression fractures, a retrospective cohort study

Zhipeng Chen[1,2#], Wei Lin[1,2#], Shengli Zhao[1,2], Xiaoyi Mo[1,2], Weiquan Yuan[1,2], Wing Hoi Cheung[3], Dan Fu[4], Bailing Chen[1,2]

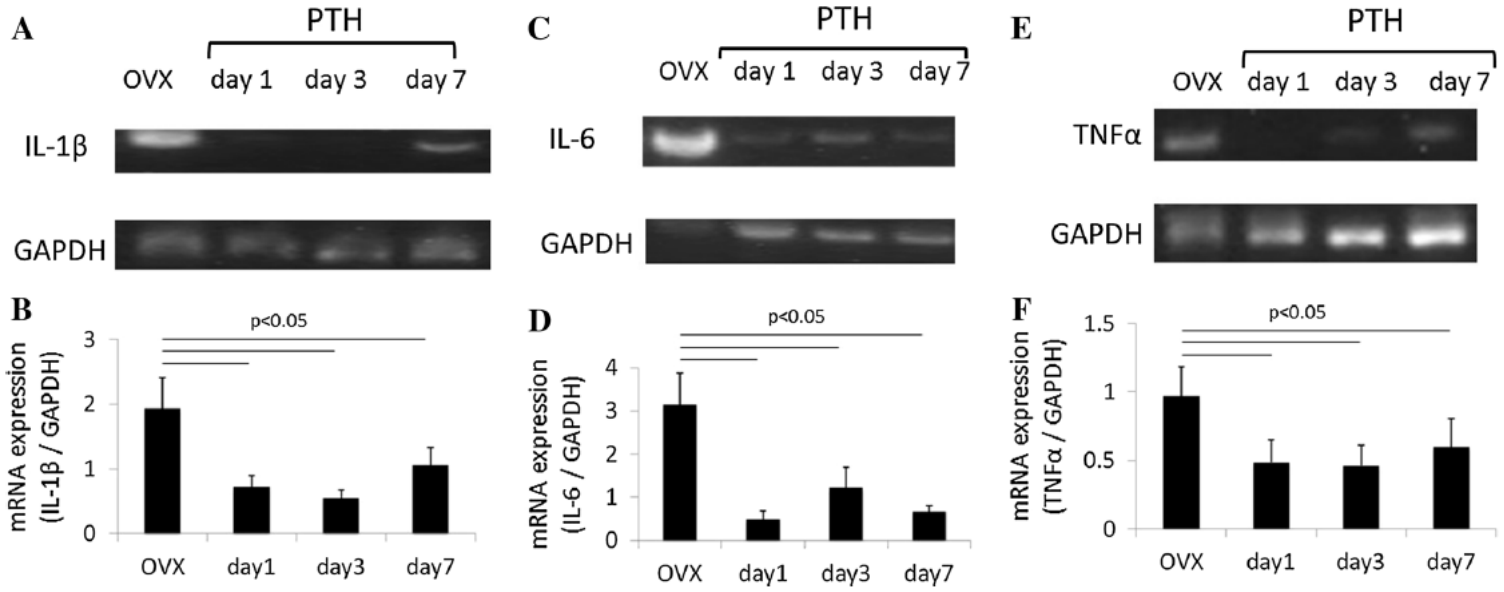


J Bone Miner Metab (2018) 36:499–507
https://doi.org/10.1007/s00774-017-0865-0

ORIGINAL ARTICLE

Teriparatide rapidly improves pain-like behavior in ovariectomized mice in association with the downregulation of inflammatory cytokine expression

Takayuki Dohke[1] · Kousuke Iba[1] · Megumi Hanaka[1] · Kumiko Kanaya[1] · Shunichiro Okazaki[1] · Toshihiko Yamashita[1]



Teriparatide relieves ovariectomy-induced hyperalgesia in rats, suggesting the involvement of functional regulation in primary sensory neurons by PTH-mediated signaling

Tomoya Tanaka[1,2], Ryoko Takao-Kawabata[1*], Aya Takakura[1,2], Yukari Shimazu[1], Momoko Nakatsugawa[1], Akitoshi Ito[1], Ji-Won Lee[2,3], Koh Kawasaki[1] & Tadahiro Iimura[2,3*]

Clinical studies have reported that teriparatide (TPTD), a human parathyroid hormone analog, reduces back pain in osteoporotic patients. However, the mechanistic insights of this pharmacological action remain elusive. This study investigated the antinociceptive effect of TPTD mainly on primary sensory neurons in ovariectomized (OVX) rats. The plantar test showed thermal hyperalgesia in the OVX rats, which was significantly, but not fully, recovered immediately after the initial TPTD administration. The von Frey test also demonstrated reduced withdrawal threshold in the OVX rats. This was partially recovered by TPTD. Consistently, the number and size of spinal microglial cells were significantly increased in the OVX rats, while TPTD treatment significantly reduced the number but not size of these cells. RNA sequencing-based bioinformatics of the dorsal root ganglia (DRG) demonstrated that changes in neuro-protective and inflammatory genes were involved in the pharmacological effect of TPTD. Most neurons in the DRG expressed substantial levels of parathyroid hormone 1 receptor. TPTD treatment of the cultured DRG-derived neuronal cells reduced the cAMP level and augmented the intracellular calcium level as the concentration increased. These findings suggest that TPTD targets neuronal cells as well as bone cells to exert its pharmacological action.

Clinical Interventions in Aging 2019:14 1693–1703

Clinical Interventions in Aging

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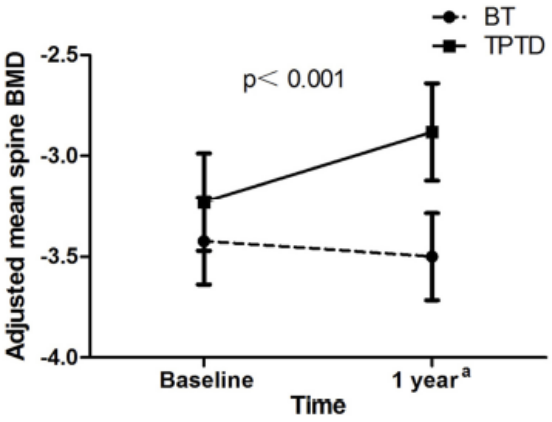
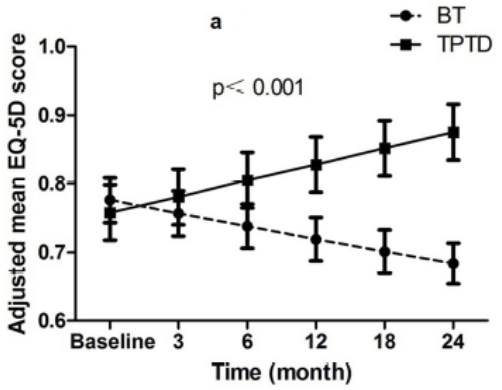
Open Access Full Text Article

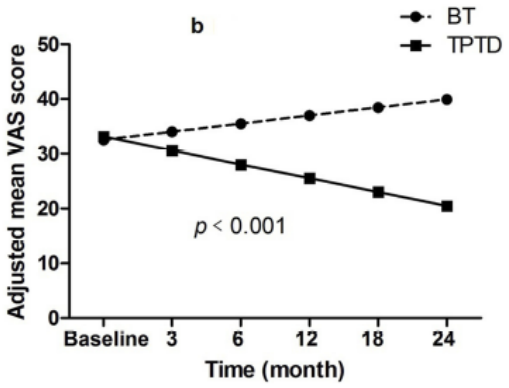
ORIGINAL RESEARCH

12-Month Teriparatide Treatment Reduces New Vertebral Compression Fractures Incidence And Back Pain And Improves Quality Of Life After Percutaneous Kyphoplasty In Osteoporotic Women

Meng Kong[1,2]
Chuanli Zhou[1]
Kai Zhu[1]
Yiran Zhang[1]
Mengxiong Song[1]
Hao Zhang[1]
Qihao Tu[1]
Xuexiao Ma[1,2]







Bone 131 (2020) 115154

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Full Length Article

Effects of teriparatide versus percutaneous vertebroplasty on pain relief, quality of life and cost-effectiveness in postmenopausal females with acute osteoporotic vertebral compression fracture: A prospective cohort study

Yangyang Ma[a,1], Xiaoliang Wu[a,1], Xiao Xiao[a], Yao Ma[a], Lan Feng[a], Wenjuan Yan[b], Jianting Chen[a], Dehong Yang[a,*]

Table 1
Options for the treatment of acute OVCF

Options	Fracture	Pain control	Osteoporosis management	Main possible complications	Cost (about)
Alendronate + analgesics	Self-healing	Analgesics, > 3 weeks	Inhibit bone resorption	Unhealed fracture, Vertebrae collapse	¥4000
PVP + alendronate	Material filling	Down to mild/moderate pain soon post op	Inhibit bone resorption	Cement leakage, Cement emboli	¥30,000–40,000 (covered by insurance)
Teriparatide + analgesics	Enhanced self-healing	Analgesics, about 2 weeks	Increase bone formation	Daily injection, May need PVP later	¥30,000–40,000 (estimated 6-month injection)
PVP + Teriparatide	Material filling	Down to mild/moderate pain soon post op	Increase bone formation	associated with PVP and teriparatide	PVP cost plus Teriparatide cost

Bone 131 (2020) 115154

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Full Length Article

Effects of teriparatide versus percutaneous vertebroplasty on pain relief, quality of life and cost-effectiveness in postmenopausal females with acute osteoporotic vertebral compression fracture: A prospective cohort study

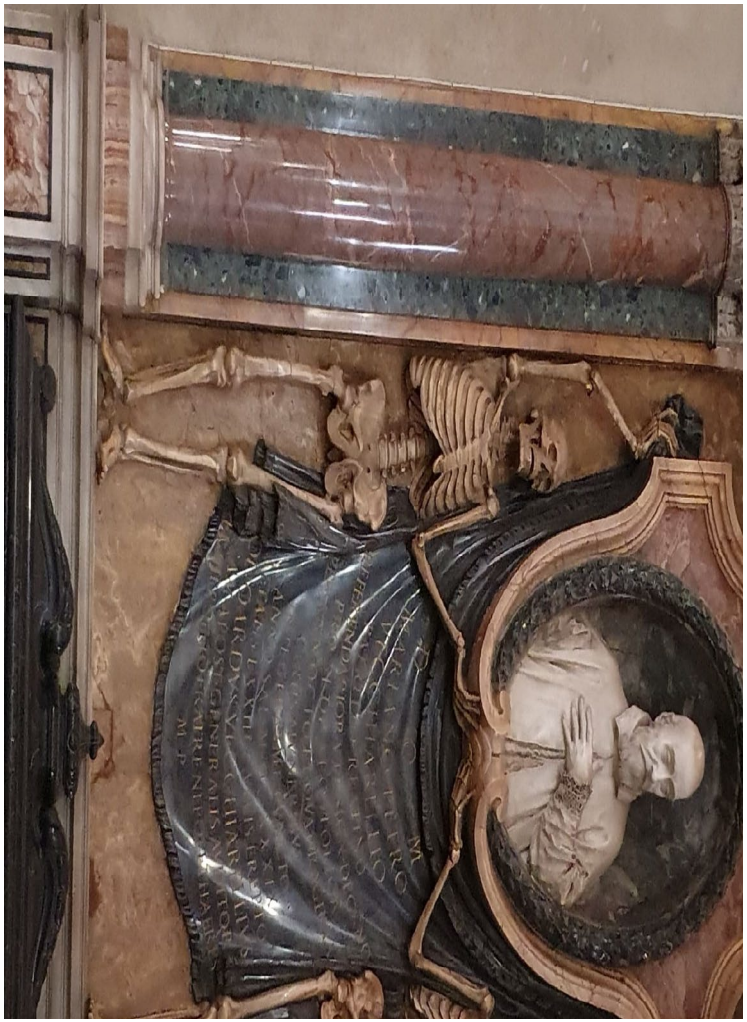
Background: Osteoporotic vertebral compression fracture (OVCF) is a common disease in senior patients. Conservative treatments (usual care) and percutaneous vertebroplasty (PVP) are typically applied to treat OVCFs; however, their efficacies are not fully satisfactory. While Teriparatide (TPTD) is effective in both anti-osteoporosis and bone healing, whether TPTD could be applied as a conservative treatment for acute OVCFs remains unclear.

Methods: This investigation represents a real-world prospective cohort study, where 60 postmenopausal women (≥55 years old) with acute OVCFs were equally assigned to a TPTD conservative group or PVP (plus alendronate) group based on the patient's choice. TPTD (20 μg, s.c., once daily) or alendronate (70 mg, p.o., once weekly) were administrated together with 0.6 mg Caltrate and 500 iu Vitamin D3 per day. A health survey (SF-36) was conducted at 0-, 1- and 3-months post-treatment. Back pain and the Oswestry Disability Index (ODI) were measured at 0-week, 1-week, 1-month and 3-months after treatment, while the direct medical cost was analyzed at the end of the third month.

Results: Both treatments with TPTD and PVP significantly and similarly improved the patients' health quality, with reduced visual analogue and ODI scores at the end of the first and third months. PVP was more effective in reducing pain at the early time point (1 week, $p < 0.05$). 24 of 27 patients who were rescanned with magnetic resonance imaging in the TPTD group showed bone healing. The mid-vertebral height was increased by PVP ($p < 0.05$) but not by TPTD. The cost of TPTD treatment was 21,868.61 ± 167.05 RMB per capita, while the cost for PVP treatment was 33,265.95 ± 1491.11 RMB per capita ($p < 0.05$).

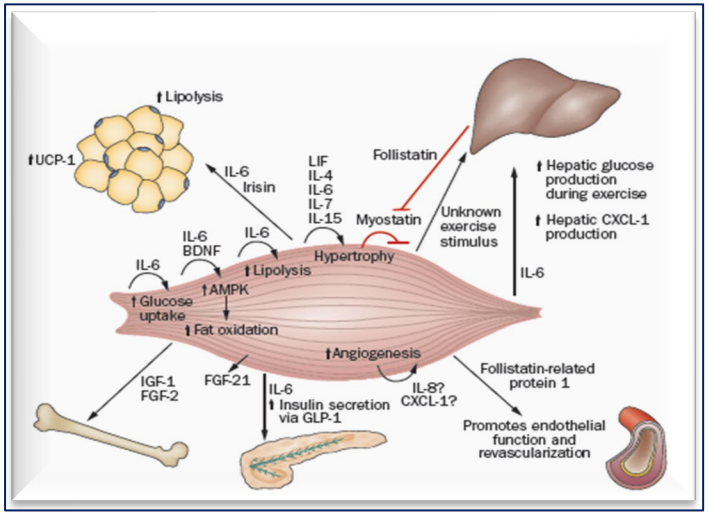
Conclusion: TPTD conservative treatment obtained similar therapeutic effects but cost less than PVP in terms of treating acute OVCF.

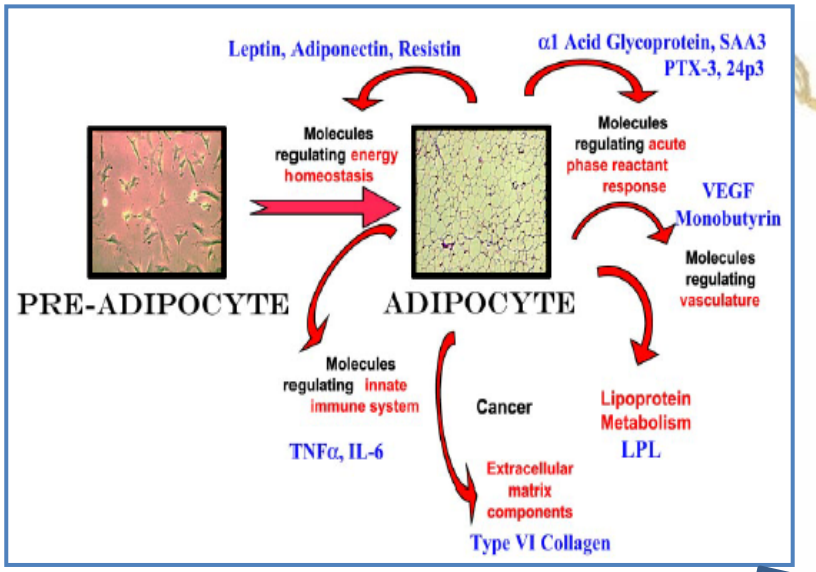
Basilica di San Pietro in Vincoli, Roma

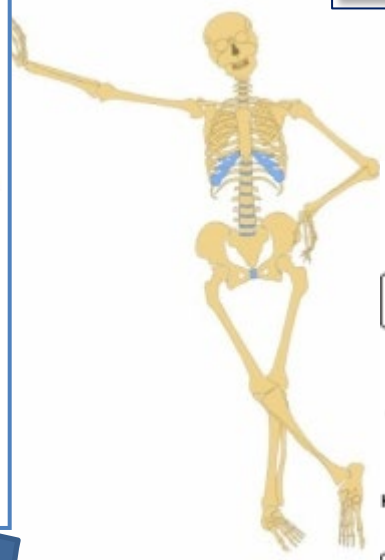


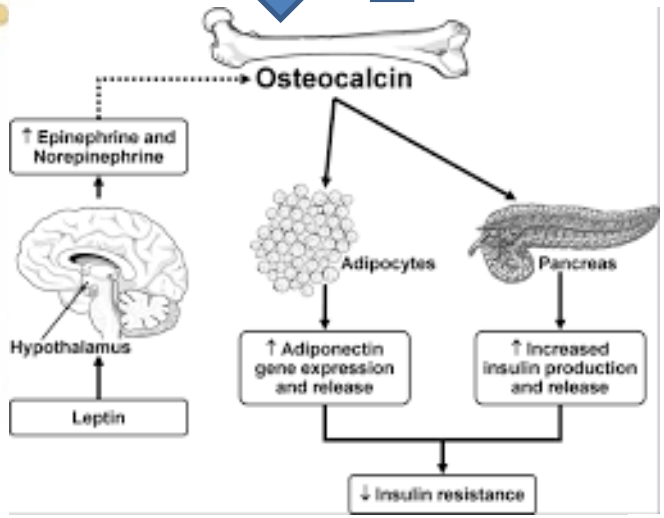
Tissues Interactions and cross-talks

Adipose Tissue
Skeletal Tissue
Muscle Tissue

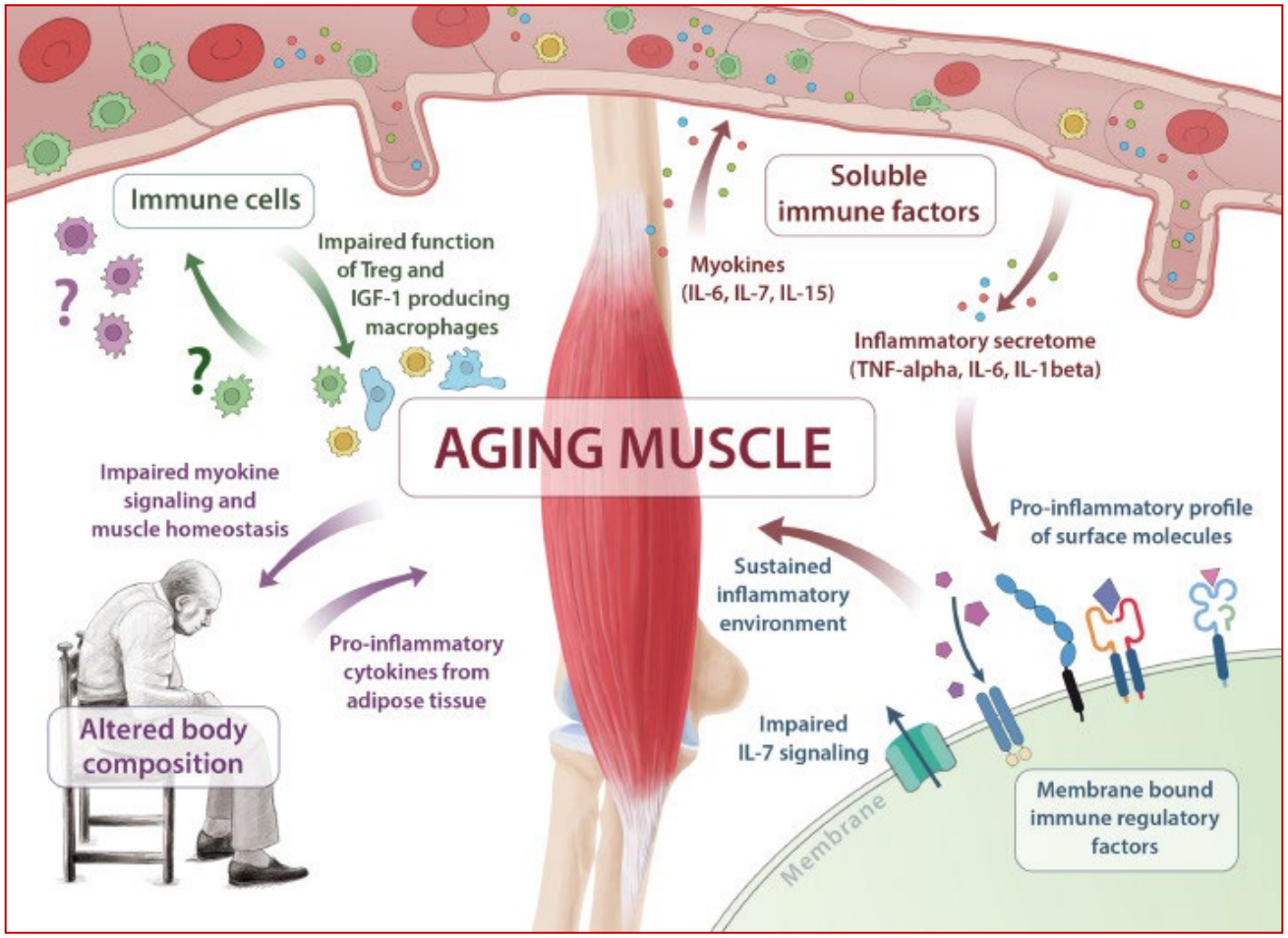






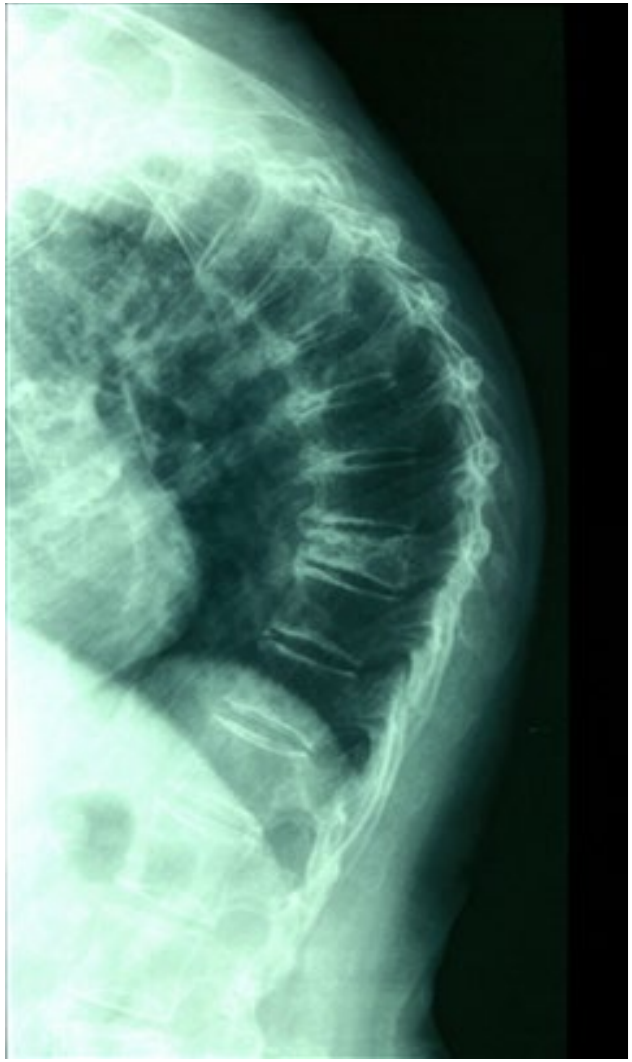


The aging muscle



Clinical of Vertebral Fracture

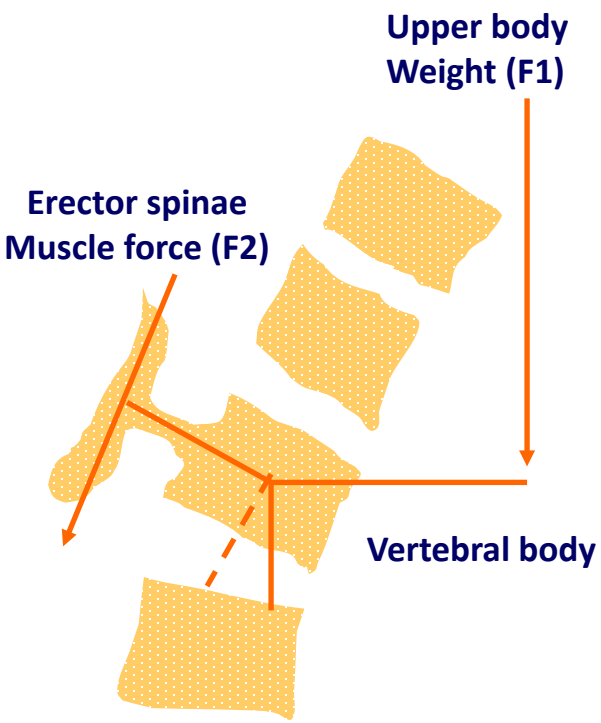
The thoracic kyphosis is most pronounced at the mid-thoracic region so that loading in flexion is accentuated



Cooper C et al, Bone 1993; 14: S89-97

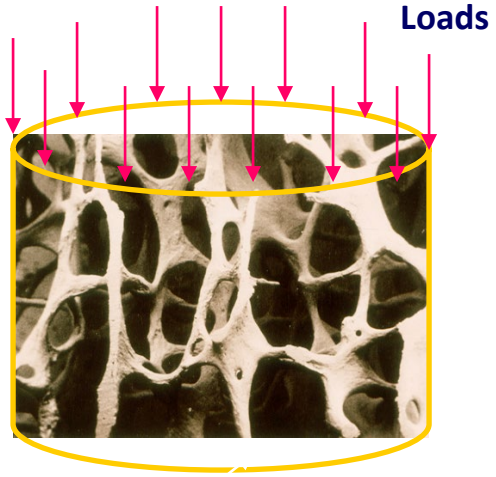
The Influence of a Load on Fracture Risk

Stress (Load per unit CSA)

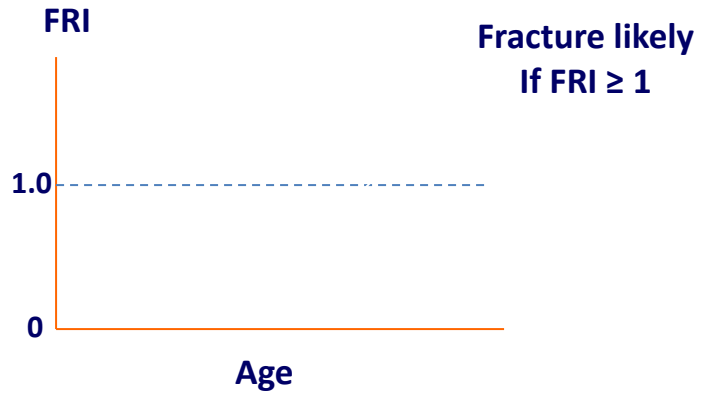


Bending Forward

Fracture Risk Index (FRI)



Structural Capacity
(vBMD x CSA)

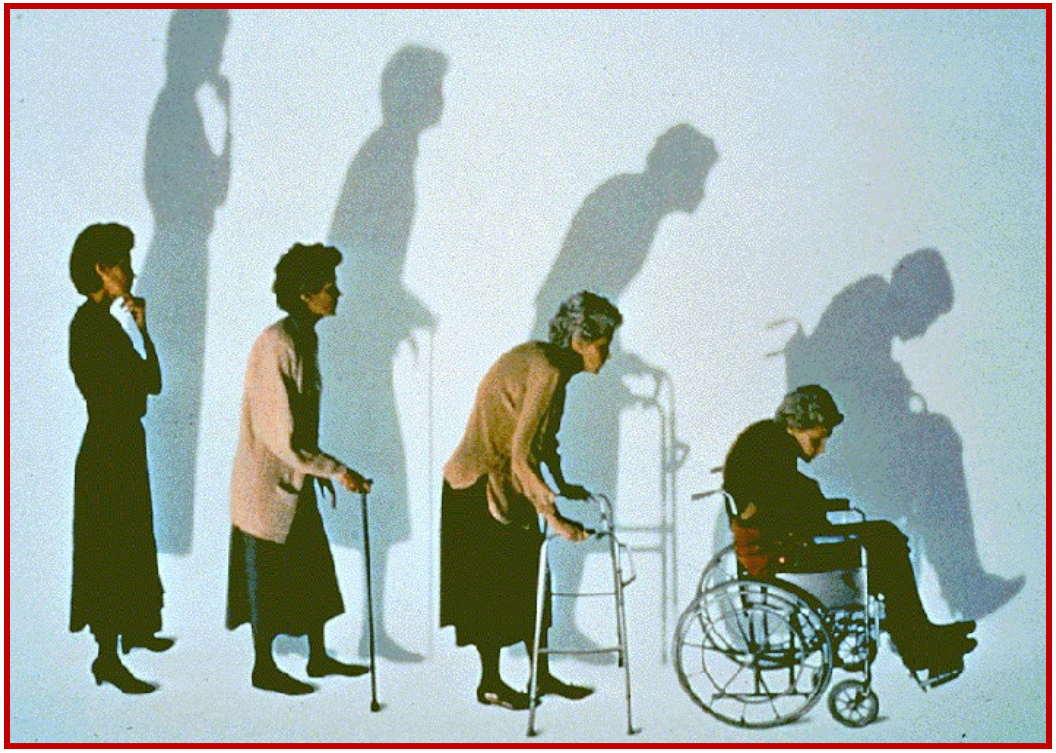


Duan Y et Al, Osteopor Int 2006; 17: 54-60

Back Pain and Vertebral Fractures

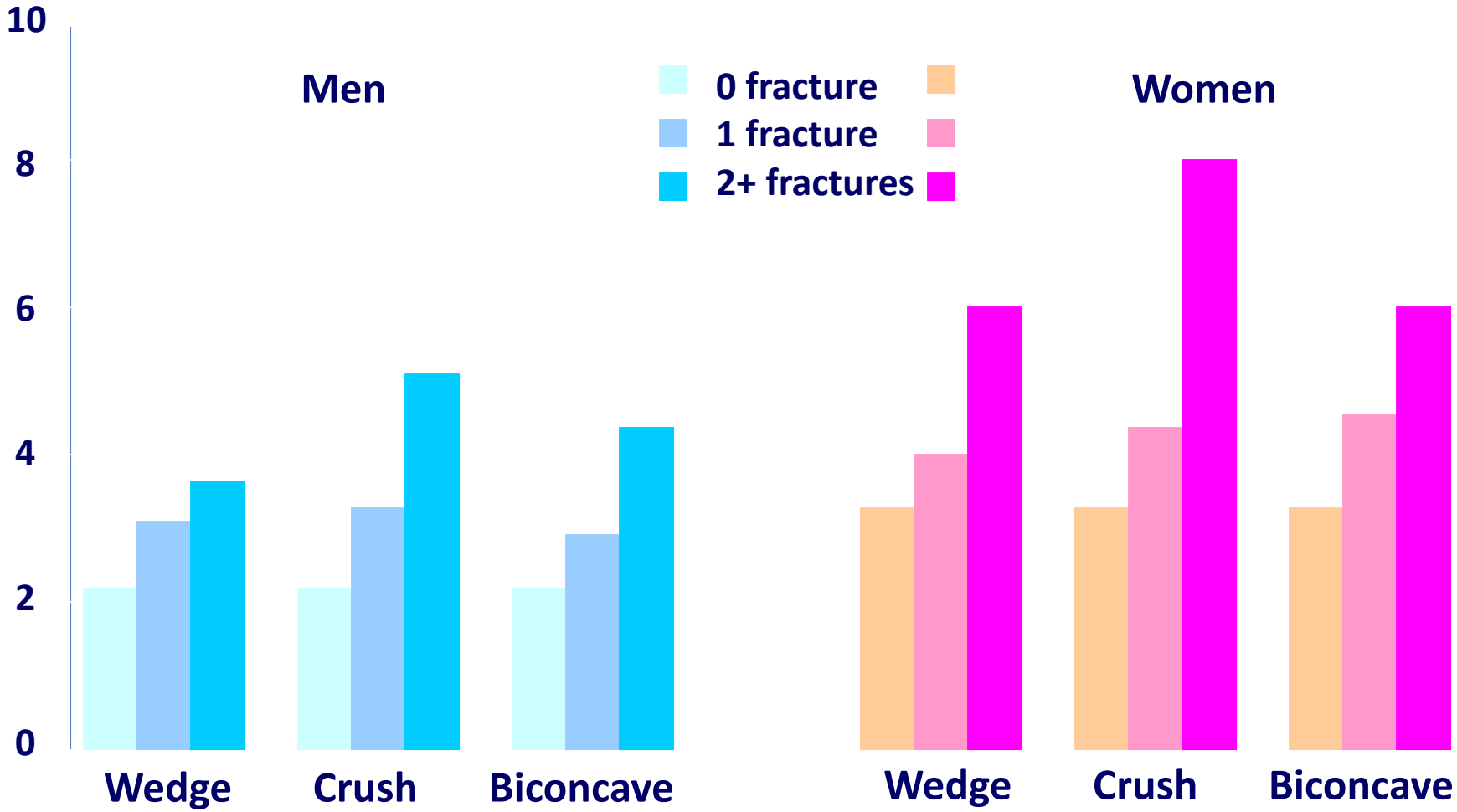
Back pain associated with vertebral fractures contribute to decreased quality of life.

The decrease in quality of life increases with each subsequent fracture, with a steep drop after the second vertebral fracture.



Silverman SL, Arthritis Rheum 2001; 44: 2611-9

Loss of height by type and number of vertebral deformities in men and women



AA Osteoporos Int 1999; 9: 206-213