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vivo in Animals and in Men - A view
into the future**

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Bone Structures *in vitro* and *in vivo* in Animals and in Men – A view into the future

M. A. Dambacher¹, S. Schmitt², E. Schacht¹, M. Ito³, M. Neff⁴, R. Müller⁵, L. Qin⁶, Y. L. Zhao⁷

Das Ziel einer Osteoporose-Behandlung ist die Reduzierung der Frakturrate. Eine erfolgreiche Osteoporose-Behandlung zielt ab auf:

- die Reduktion der Frakturrate, sowohl bei vertebrealen als auch bei nichtvertebralen Lokalisationen,
- die Erhaltung der Knochenmasse und
- die Erhaltung der Integrität der Knochenmikroarchitektur.

Die Diskrepanz zwischen den Anstieg der Knochendichte unter der Behandlung und der Reduktion des Frakturrisikos ist noch nicht voll geklärt, eine große Rolle spielt jedoch die Mikroarchitektur.

The primary target of an osteoporosis treatment is a reduction in fracture rate. A successful therapy is

- leading to a reduced fracture risk at both vertebral and non-vertebral sites,
- preserving bone mass and
- preserving the integrity of bone microarchitecture.

The discrepancy between increase of bone density under therapy and decrease in fracture risk is not yet fully explained. *J Miner Stoffwechs* 2004; 11 (3): 13–19.

Osteoporosis has often been defined as a disease of decreased bone mass leading to fragile bones and finally fractures. The measurement of bone mass or bone density is still the major diagnostic tool to detect osteoporotic patients or patients at risk. Treatment options as well were for many years selected on their ability to increase bone mass, the more the better. But over the last few years definitions and discussions of what constitutes osteoporosis have changed from single important criterion “bone mass” to a more sophisticated approach of bone strength. According to the most recent National Institutes of Health (NIH) consensus statement, osteoporosis is defined as a skeletal disorder characterized by compromised bone strength that results in an increased risk of fracture [1]. But what is meant by the term bone strength?

The Bone Quality Discussion Group met in 2000 to discuss the various components of bone strength and their relevance for fracture risk in osteoporosis [2]. They postulated that bone strength is determined by both bone quantity and bone quality. Bone quantity (mainly bone mass and size) is only one contributing factor (Tab. 1). The other, bone quality, comprises various parameters like the three-dimensional arrangement of bone material with respect to macroarchitecture (bone geometry) and microarchitecture (e. g. trabecular connectivity), the mechanical properties of bone material (e. g. mineralization, microfractures, collagen cross-linking) and bone turnover. Especially the micro-architectural changes in osteoporosis have become an important factor responsible for the increase in fracture risk. But how to measure these parameters in osteoporotic patients?

Areal and volumetric bone mass can be measured non-invasively by different X-ray based methods as DXA and QCT (pQCT, microCT). To assess 3D trabecular bone

structures qualitatively and quantitatively, microCT has emerged as the leading technique for in-vitro examinations, high-resolution peripheral QCT (hrpQCT) for in-vivo examinations. With this technique (e. g. MicroCT Scanco Medical AG, Zuerich, Switzerland) bone microarchitecture of bone samples can be imaged with a spatial resolution (voxelsize) down to 5 micrometers; with hrpQCT in-vivo (patients) down to 100 µm and in animals in vivo to 15 µm.

A 3D quantitative evaluation includes the bone volume fraction (BV/TV), trabecular number (Tb.N), trabecular and cortical thickness (Tb.Th) and trabecular separation (Tb.Sp), degree of anisotropy, connectivity density, structure model index (rod vs. plate characteristics), bone surface ratios etc. Volumetric bone density (vBMD) of trabecular and cortical bone can also be measured separately (Figs. 1, 2).

Figure 3 shows sections (tibia) of 25 µm in thickness of the same animal scanned at week 0, 2 and 8 after OVX. Changes in bone density (bone volume fraction) and changes in bone microarchitecture can be measured with high precision (reproducibility better than ± 0.2 %). 3D analysis revealed that over 8 weeks only bone volume fraction dropped more than 50 %. Also a decrease in trabecular number of 40 % and a slight reduction in trabecular thickness of 25 % was observed.

Table 1: BMD-increase under treatment is not parallel to fracture-risk reduction

Studies (3 years)	Δ BMD (%) vs. controls	% vertebral fracture risk reduction
Calcitonin (PROOF) [Chesnut et al., Am J Med 2000]	0.5	36
Raloxifene (MOORE) [Ettinger et al., JAMA 1989]	2.6	30
Alendronate (FIT-1) [Black et al., Lancet 1996]	6.2	47
Risedronate (VERT-NA) [Harris et al., JAMA 1999]	4.3	41
Risedronate (VERT-MN) [Reginster et al., Osteoporos Int 2000]	5.9	49
Fluoride (FAVOS 2 years) [Meunier et al., Osteoporos Int 1998]	8.4	no difference to placebo

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Risedronate

For the following analyses of biopsies of an animal study a μ CT-Scanner was used (Scanco Medical AG, Zürich, Switzerland). The results of the analysis were published by Borah et al. in 2002 [3]. In this study female minipigs were fed with a calcium-restricted diet from 4 months of age and ovariectomized or sham-operated at ~18 months of age (a model for postmenopausal osteoporosis) followed by a treatment of either risedronate (2.5 mg/kg) or placebo for another 18 months and the biomechanical properties of trabecular vertebral bones were investigated. After necropsy, L4 vertebral cores were prepared from all animals. The trabecular architecture was evaluated by μ CT (Scanco Medical AG, Zürich, Switzerland) and bone strength analyzed by biomechanical compression testing. The architectural measurements trabecular thickness, trabecular number, connectivity (connectivity density) and Bone Volume/Tissue Volume (BV/TV, %) had significantly increased after 18 months of risedronate treatment (2.5 mg/kg) compared to placebo ($p \leq 0.05$), as analysed at the end- and midsection of the vertebral specimens. Furthermore the treatment group showed a significant decrease of the Marrow Star Volume (a measure for bone porosity) and trabecular separation ($p < 0.05$). As revealed by the μ CT images, the relative amount of trabecular bone orthogonal to the cranial-caudal axis was higher in the risedronate-treated vertebra specimens compared to the placebo-treated.

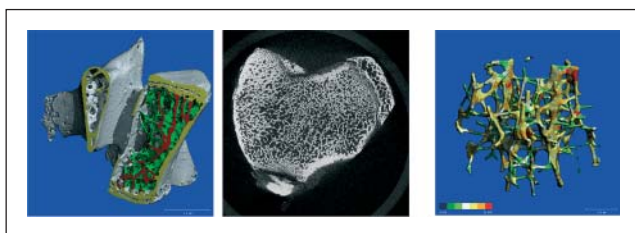


Figure 1: Mouse vertebra, rat tibia and lumbar vertebra (biopsy) of a 85 year old man (MicroCT20, Scanco Medical AG, Zuerich, Switzerland)

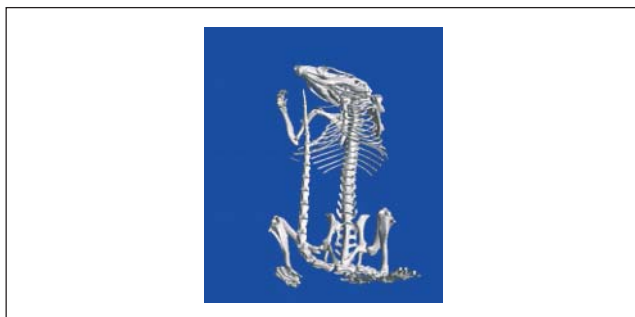


Figure 2: Anatomical image of a mouse skeleton measured with microCT, 36 μ m resolution (MicroCT20, Scanco Medical AG, Zuerich, Switzerland)

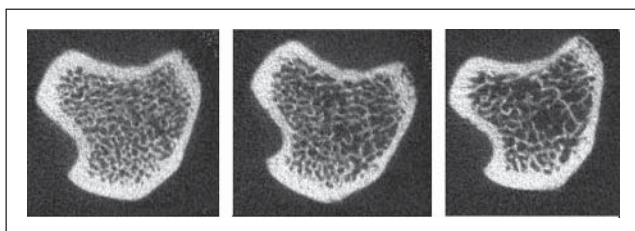


Figure 3: Sections of the tibia (same rat) at week 0, week 2 and week 8 (VivaCT20, Scanco Medical AG, Zuerich, Switzerland, mit freundlicher Genehmigung von Dr. J. Gasser, Novartis Basel)

This observation was quantitatively confirmed by a significant increase in the % cross-strut. The subsequently performed mechanical testing showed a significantly higher maximum load (strength) and stiffness for the risedronate-treated vertebra specimen than for the placebo-treated ($p < 0.05$). These results support the strong correlation between bone architecture and bone strength (Figs. 4–6) [3].

Similar findings of preservation of bone microarchitecture under risedronate treatment have been seen in a study in early postmenopausal women recently published by Dufresne et al. [4]. Bone biopsy samples from 39 women enrolled in a 2-year, double-blind, placebo-controlled study (entire cohort $n = 64$) with risedronate to evaluate the effects on BMD in early postmenopausal women were collected at baseline and after 1 year of treatment. The objective of this study was to determine, by 3D μ CT (μ CT-20,

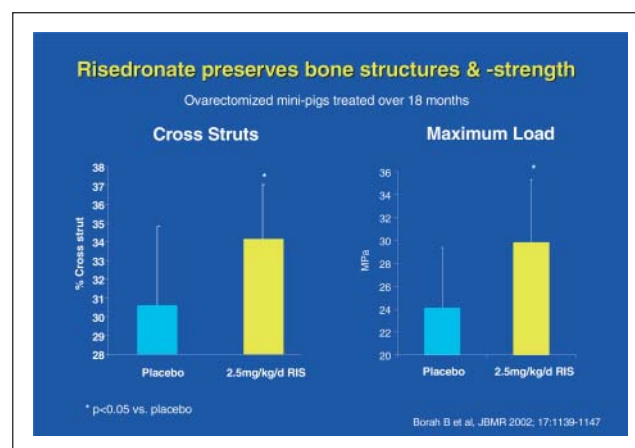


Figure 4: Risedronate preserves bone structure & strength: Ovariectomized mini-pigs treated over 18 months (Reproduced from [3], with permission of the American Society for Bone and Mineral Research)

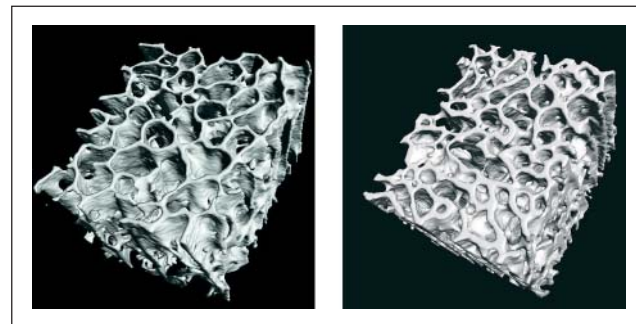


Figure 5: Architecture in minipig vertebra after 18 months of treatment (Reproduced from [3], with permission of the American Society for Bone and Mineral Research)

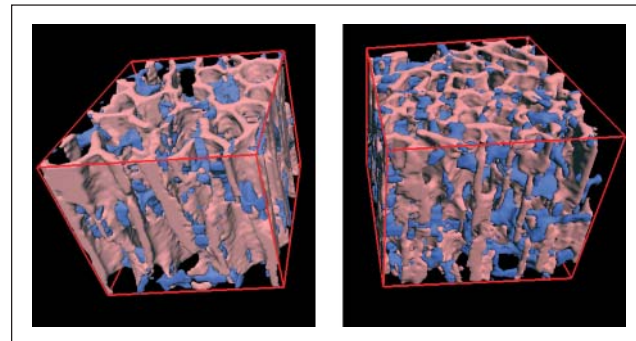


Figure 6: Horizontal trabeculae are maintained by risedronate (Reproduced from [3], with permission of the American Society for Bone and Mineral Research)

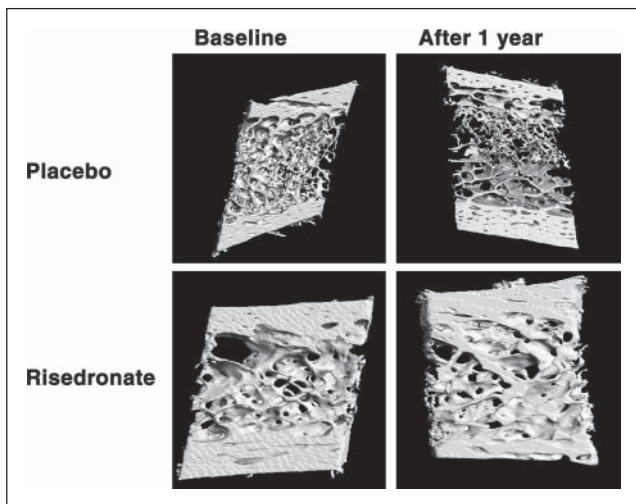


Figure 7: Representative MicroCT images of paired iliac crest biopsies of a placebo group patient and a risedronate patient at baseline and after 1 year (Reproduced with permission from [4], © Springer)

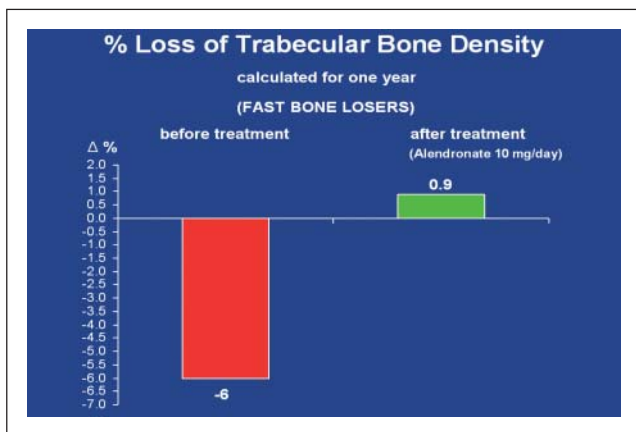


Figure 8: Alendronate: % Loss of trabecular bone density calculated for one year, fast bone loser

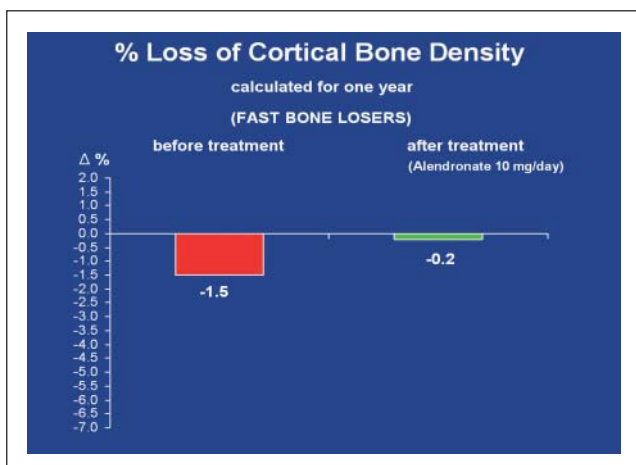


Figure 9: Alendronate: % loss of cortical bone density calculated for one year, fast bone loser

Scanco Medical AG, Zürich, Switzerland), the effects of a 1-year therapy of risedronate 5 mg daily on trabecular and cortical architecture in early postmenopausal women (6–60 months) who were not osteoporotic at the start of the study (T-score > -2 SD, no prevalent vertebral fracture). Patient characteristics at baseline were balanced between the treatment groups with LS BMD T-scores being marginally osteopenic. Results showed LS-BMD decrease under

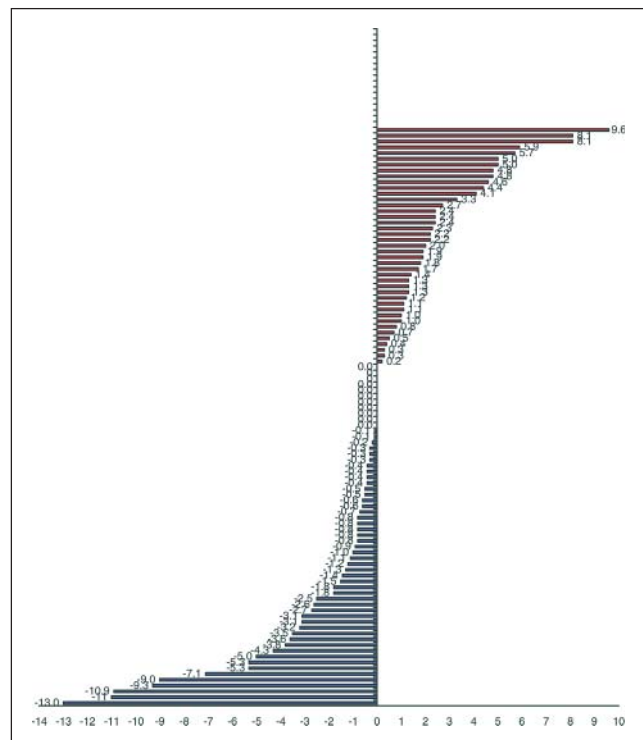


Figure 10: $\Delta\%$ trabecular bone density, first year, alendronate 10 mg/day

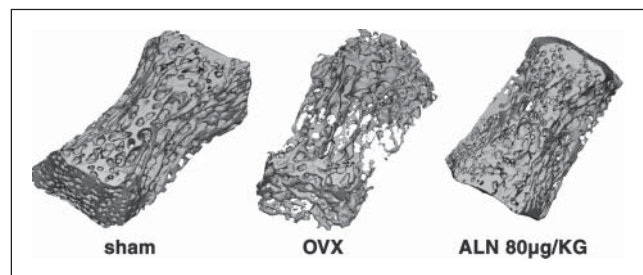


Figure 11: Alendronate: Bone biopsies of rats 3-dimensional (Reprinted with permission from [5], © 2003 Elsevier)

placebo after 1 year, but an LS-BMD increase under risedronate treatment ($p < 0.0001$ between groups). For a number of key architectural parameters, 1 year of placebo treatment revealed marked deterioration. Compared to baseline, both bone volume (BV/TV) and trabecular number (Tb.N.) decreased ($p = 0.034$, $p = 0.052$), while trabecular separation (Tb.Sp.) and Marrow Star Volume (a measure for bone porosity) increased ($p = 0.056$, $p = 0.04$).

In contrast to these findings, bone samples from the risedronate-treated women showed preservation of these structural elements. Comparison of the changes from baseline in the risedronate treatment group with those under placebo treatment demonstrated that bone volume, trabecular thickness and trabecular number significantly increased in risedronate group ($p = 0.01$, $p = 0.03$, $p = 0.01$) whereas parameters for bone porosity like trabecular separation ($p = 0.01$) and Marrow Star Volume ($p = 0.04$) increased significantly in the placebo group.

These results prove the findings from other studies that bone loss is accelerated, especially in early menopause, primarily due to high bone turnover, leading to rapid deterioration of bone microarchitecture with increased fracture risk. This study has furthermore demonstrated that risedronate can not only halt bone loss in early menopause but

Table 2: Alendronate in rats (Reprinted with permission from [5], © 2003 Elsevier)

OVX n = 30	Sham n = 6
Max Load	Increase
Trab Volume	Increase
Trab Thickness	Increase
Inter Trab Space	Decrease
Trab Number	Increase

can also prevent these structural deteriorations and preserve bone microarchitecture which could be an explanation for the rapid anti-fracture efficacy risedronate has shown in clinical trials (Fig. 7).

Alendronate

At the University Clinic Balgrist in Zurich, Switzerland, we have treated fast bone losers with the anti-resorptive alendronate (Figs. 8, 9). Fast bone losers are defined as patients who lose more than 3 % trabecular bone density/year. With our method (highly precise Quantitative Computed Tomography, Scanco Medical) which has a reproducibility in mixed collectives of ± 0.2 to ± 0.4 % we can analyze a patient with fast bone loss within 6 to 9 months. If we would be using DXA-measurement, which has a reproducibility of 1–2 %, we would need for the same result a period of 2 years. The best parameter for evaluation is the trabecular bone density of the radius.

The figures 8 and 9 show the data of trabecular and cortical bone density in fast losers before and after alendronate treatment for 9 months (figures show results extrapolated for 1 year). The data reflects that under treatment with an efficient inhibitor of bone resorption fast bone loss can be set on hold. At the University Clinic Balgrist we have furthermore treated 100 postmenopausal women with osteoporosis (WHO definition), to follow up the individual course under treatment with 10 mg/day alendronate for 1 year. The individual results in change of trabecular BMD measured by pQCT are shown in Figure 10.

In 36 % of the patients trabecular BMD increased after 1 year of alendronate treatment, in 39 % of the patients no change in BMD was measurable, in 10 % a slow and in 16 % of the patients a fast loss of trabecular bone density was still evident.

In an animal study on ovariectomized rats, treated with alendronate 80 mg/kg for 24 weeks, bone biopsies were again analyzed with a μ CT-Scanner (microCT20, Scanco, Zurich, Switzerland). Results on bone density and bone structures under treatment compared with the OVX rats are summarized in the Table 2 and Figure 11. This study of Ito (Nagasaki) shows that bone loss in these ovariectomized animals could be eliminated with alendronate [5].

Alfacalcidol

Established osteoporosis in older patients of both sexes is characterized by lack of vitamin D and reduced synthesis of D-hormone (calcitriol; $1,25(\text{OH})_2\text{D}$) in kidneys and bone as well as by lack of receptors (VDR's) and/or receptor affinity for D-hormone in the target organs.

Alfacalcidol is activated in the liver and in other target organs like bone and is a so-called prodrug of D-hormone

(Calcitriol). D-hormone deficiency can be treated therefore through by-passing the physiological regulation in the kidney. Vitamin D resistance based on VDR-deficits can also be treated by D-hormone analogues through their influence on expression and activation of VDR's.

Alfacalcidol induces absorption of calcium and phosphate in the intestine, supports mineralization of bone and facilitates normal neuromuscular functioning. The D-hormone analogue indirectly suppresses PTH, which is particularly high in elderly patients, through increased calcium absorption but also directly by inhibition of the proliferation of the parathyroid gland, as well as of PTH synthesis and release. D-hormone also reduces the release of pro-inflammatory cytokines, which are partly increased in elderly and are factors for osteoclast activation and bone resorption.

New findings show that alfacalcidol inhibits osteoclastogenesis in vivo by decreasing the pool of osteoclast precursors in bone marrow which could explain the direct inhibition of D-hormone analogues on bone resorption [6]. Furthermore D-hormone analogues have very specific T-cell immunoregulating properties and induce cytokine homeostasis by decrease of pro-inflammatory and increase of anti-inflammatory cytokines. D-hormone analogues have shown to increase BMD and reduce vertebral and non-vertebral fractures in prospective, randomized, mainly placebo-controlled studies [7–9].

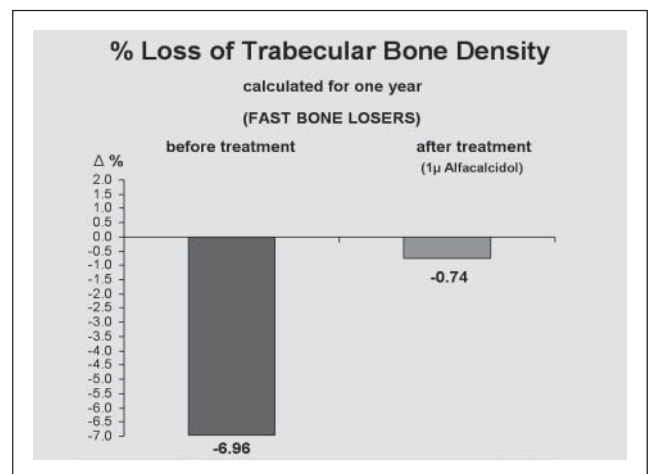


Figure 12: Alfacalcidol: % Loss of trabecular bone density calculated for one year, fast bone loser

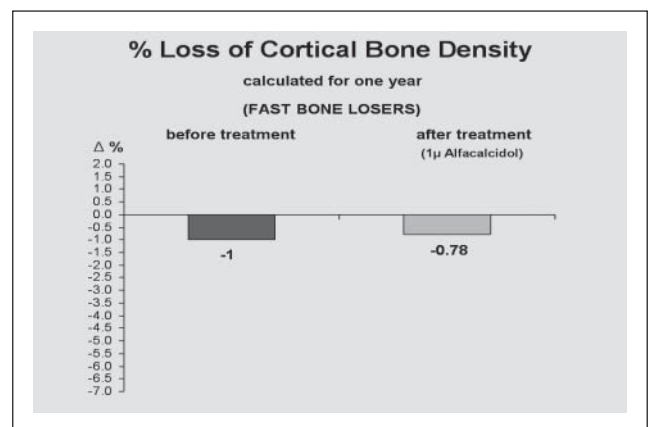


Figure 13: Alfacalcidol: % loss of cortical bone density calculated for one year, fast bone loser

It is also important to know that D-hormone protects osteoblasts in vitro against TNF- α -induced apoptosis. This mechanism has been demonstrated in vivo in the inflammation-mediated osteopenia (IMO) model, an animal model that simulates bone loss in rheumatoid arthritis [10]. D-hormone analogs have very specific T-cell immunoregulating properties and inducing cytokine homeostasis by decrease of pro-inflammatory and increase of anti-inflammatory cytokines [11, 12].

Alfacalcidol is very effective in reducing the fast bone loss which is identical with a high bone turnover in postmenopausal women. Figures 12 and 13 show the data of trabecular and cortical bone, respectively, in fast losers after alfacalcidol treatment of 9 months (calculated for 1 year): it allowed us to eliminate the fast bone loss.

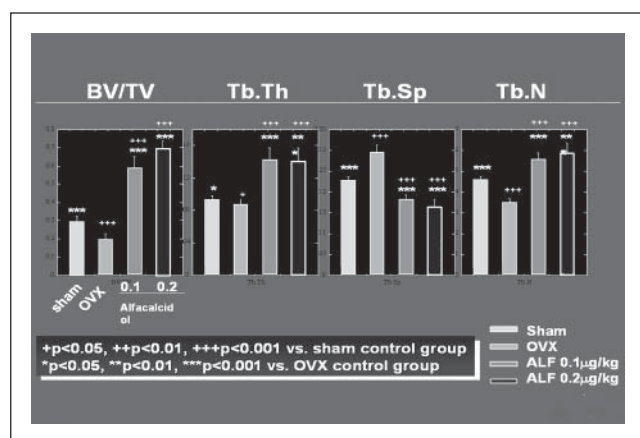


Figure 14: Alfacalcidol: Results on bone density and bone structures (Reprinted with permission from [5], © 2003 Elsevier)

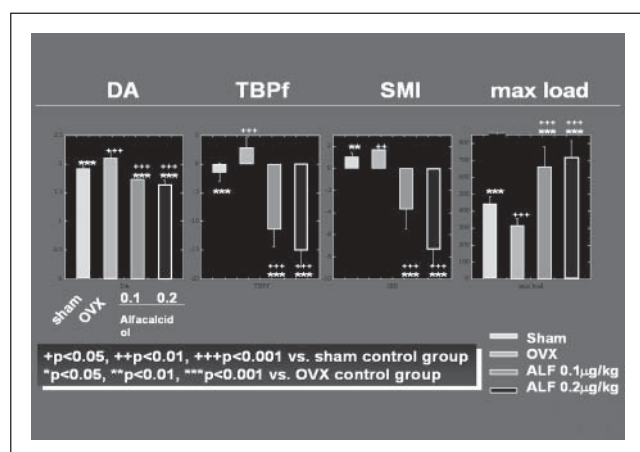


Figure 15: Alfacalcidol: Results on bone density and bone structures (Reprinted with permission from [5], © 2003 Elsevier)

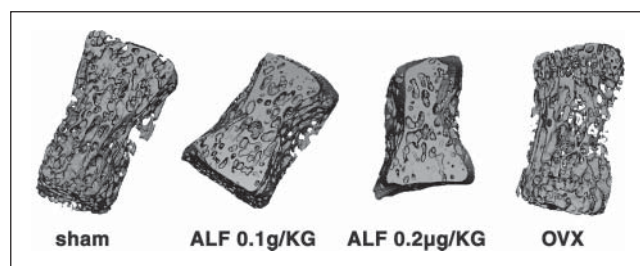


Figure 16: Alfacalcidol: Bone biopsies of rats 3-dimensional (Reprinted with permission from [5], © 2003 Elsevier)

Table 3: Alfacalcidol in rats (Reprinted with permission from [5], © 2003 Elsevier)

OVX n = 48	Sham n = 14
Max Load	Increase
Trab Volume	Increase
Trab Thickness	Increase
Inter Trab Space	Decrease
Trab Number	Increase

In an animal study [5] on ovariectomized rats treated with alfacalcidol 0.1 and 0.2 µg/kg four months bone biopsies were again analyzed with a µCT-Scanner (microCT20, Scanco, Zurich, Switzerland). Results on bone density and bone structures under treatment compared with the OVX rats are shown in the Figures 14–16 and Table 3. This study of Ito (Nagasaki) shows that bone loss in these ovariectomized animals could be stopped with alfacalcidol [5].

PTH

Parathormone (PTH) is a calcium regulating hormone and consists of 84 amino-acids with an amino- and a carboxy-terminal end. The active fragment is the 1 to 34 amino-terminal end of the hormone. PTH increases the serum calcium especially by increasing bone resorption, in contrast to calcitonin which decreases serum calcium. This means that the calcium regulation is a double feedback mechanism which keeps the serum calcium constant without remarkable variations. Parathyroid hormone stimulates both bone formation and resorption leading to an increase or decrease of bone mass, depending on the frequency of

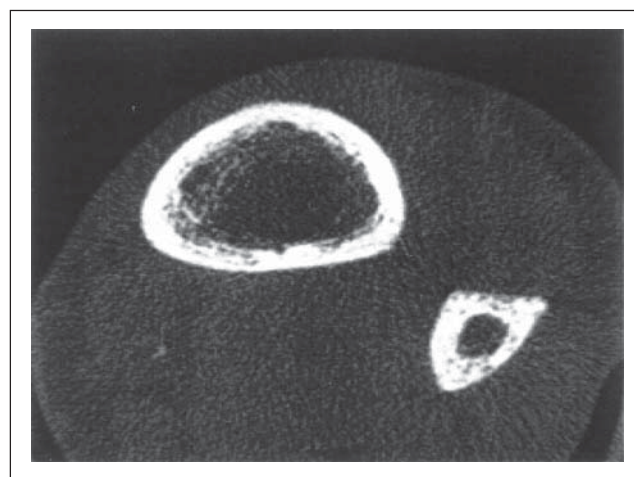


Figure 17: pHPT Tibia, Fibula, remarkable bone destruction (2D pQCT)

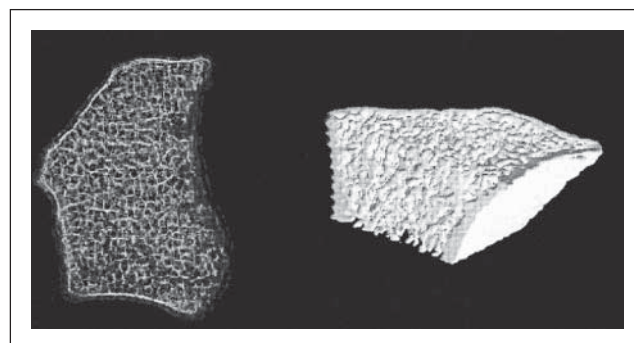


Figure 18: pHPT Radius, normal bone structures (3D pQCT)

administration. Continuous administration leading to an elevation serum PTH, like in primary hyperparathyroidism, results in an activation of bone resorption.

Figure 17 and 18 show remarkable destruction of bone in primary hyperparathyroidism (pHPT) (Computed Tomography, Radius Denscan System) (Fig. 17), but patients with pHPT may also show normal trabecular bone density (Fig. 18) (Radius, 3-Dimensional picture in vivo Denscan System).

Daily subcutaneous injections on the other hand, cause only transient elevations in serum PTH, therefore stimulating bone formation. Randomized, double-blind clinical trials have proved that in this mode of administration, daily subcutaneous injections of PTH can be used for the treatment of established osteoporosis in postmenopausal women.

Neer et al. [13] treated 1637 postmenopausal women with pre-existing vertebral fracture(s) with either placebo (n = 544) or parathyroid hormone (1-34) at a dose of 20 µg (n = 541) or 40 µg (n = 552) once daily as subcutaneous injections. Additionally patients received daily supplements of 1000 mg calcium and 400–1200 IU of vitamin D. Primary endpoint of the study was the incidence of new vertebral fractures, secondary parameters were incidence of non-vertebral fractures and change in BMD. Mean treatment duration was around 18 months in the 3 groups. The originally planned 3 year study was terminated early by the sponsor due to findings from an animal study in rats where osteosarcomas developed after long-term administration of higher dosages. New vertebral fractures occurred in 14 % of the placebo patients versus 5 % and 4 % in the 20 µg and 40 µg PTH groups, meaning a reduction in fracture risk of 65 and 69 percent ($p < 0.001$) after 21 months of treatment.

New nonvertebral fractures were classified by the local investigator as either a fragility fracture, if the associated trauma would not have led to a fracture in a normal bone, and all other nonvertebral fractures. New nonvertebral fractures occurred in 119 women and were defined as fragility fractures in 58 women. After 19 months the risk reduction of all nonvertebral fractures was 35 % in the 20 µg and 40 % in the 40 µg PTH group when compared to placebo ($p = 0.04$, $p = 0.02$). For the nonvertebral fragility fractures the

risk reduction after 19 months was 53 % and 54 %, respectively (Fig. 19). These data on vertebral and nonvertebral risk reduction under various doses of PTH show that the fracture risk reduction is not dose dependent.

On the other hand the results on BMD were significantly dose-dependent. After 19 months treatment with 20 µg PTH BMD at the spine increased by 9.7 % versus baseline, 40 µg PTH led to an increase by 13.7 %. At the hip the increase was 2.8 % and 5.1 % versus baseline, respectively. BMD at the radius decreased in all 3 groups, the decrease in the 40 µg group being significantly higher than in the placebo group ($p < 0.001$).

Application of the higher PTH dose led to a higher BMD-increase at the spine and the hip, but not to a stronger reduction of fracture risk. Teriparatide (hPTH-1-34), the generic name of the active fragment, has been approved in the US at a dose of 20 µg/day (Forsteo®) for treatment of established osteoporosis in postmenopausal women who are at high risk of fracture. Recently it has been approved in nine of the 15 EU member states as well as the non-EU countries Iceland, Norway and Switzerland for the same indication.

In a paired biopsy study [14] 8 men with idiopathic osteoporosis (average age 49 yrs) and 8 postmenopausal women with osteoporosis (average age 54 yrs) were treated with 400 IU/day PTH, 1500 mg calcium and 400 IU vitamin D daily. Women were treated for over 36 months, men for 18 months. Biopsy specimens were taken before and after treatment and analyzed via histomorphometry and microcomputed tomography (micro-CT). Histomorphometry showed a maintenance in cancellous bone area in both men and women. 3D-Micro-CT also showed a maintenance of cancellous bone volume in women and a trend towards an increase in men. There was also a trend towards an increase in connectivity density in both men and women, but the heterogeneity in the individual responses did not lead to a clear result. Nevertheless some results in single patients are quite impressive and shown below (Fig. 20). Cortical thickness was significantly increased ($p < 0.01$) in women and slightly in men. Figure 20 shows paired biopsy specimens from a 64-year old woman. The change of "cortical thickness" and "connectivity density" before and after treatment can be seen.

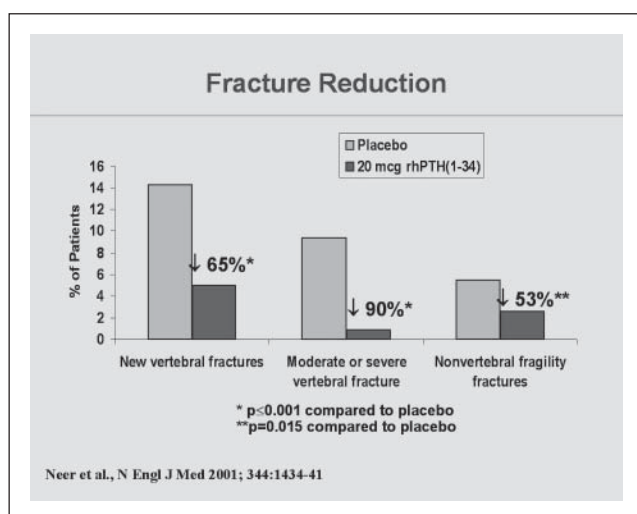


Figure 19: PTH treatment, fracture reduction (Reprint with permission from [13]. © 2001 Massachusetts Medical Society. All rights reserved.)

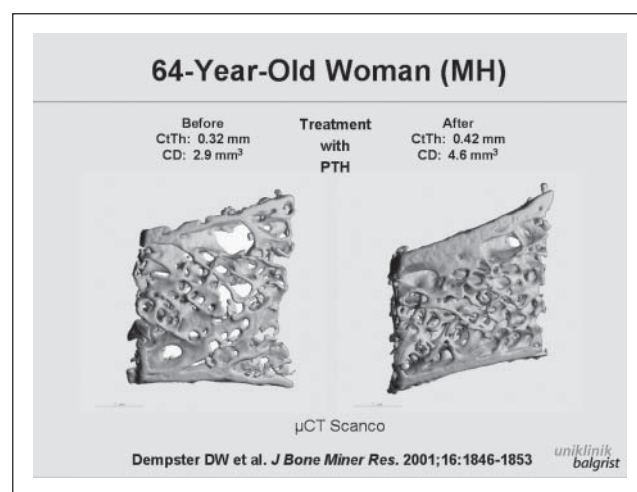


Figure 20: Paired biopsy specimens from a 64-year-old woman (Reproduced from [14] with permission of the American Society for Bone and Mineral Research)

Acknowledgement

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