Definition: Osteoporosis and Fractures

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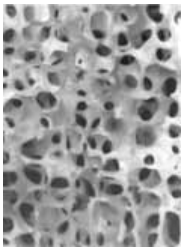
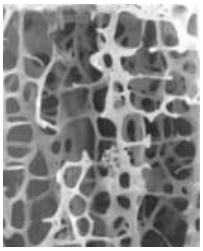
Medical University of Vienna

What is Osteoporosis ?





The Size of the Problem

Worldwide:	250 Mill.
Austria:	700 000

The Size of the Problem

Women 60 -70 yrs	33 percent
Women 80+ yrs	66 percent

Osteoporotic Fractures

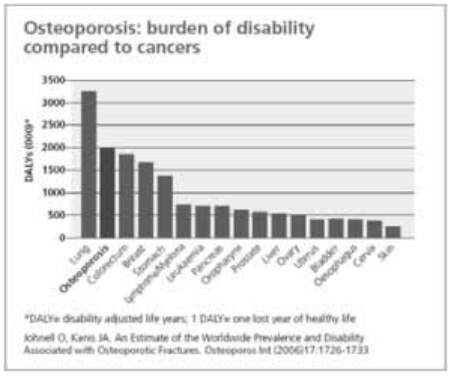
Worldwide lifetime risk for osteoporotic fractures:

Women	40 percent
Men	13 percent

International Osteoporosis Foundation

European Union Consultation Panel

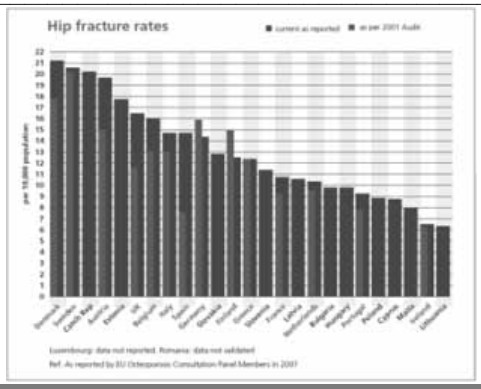
2008



„Hip Fractures“

Fractures of the proximal femur

Austria: 16272 (2006)
19,7 per 10 000 persons



„Hip Fractures“

Days in Hospital

Austria

acute care: 16,2 days
Rehabilitation: 23,0 days

„Hip Fractures“

Direct Costs

Austria

acute care: 8 104,31 EUR / Pat. (15855)

acute + Reha: 11 266,81 EUR / Pat. (417)

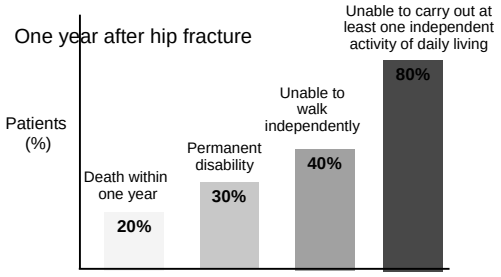
„Hip Fractures“

Austria

direct costs:

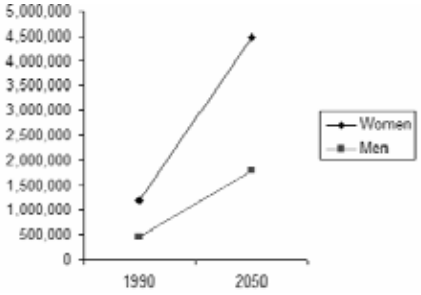
133 Million EUR

Consequences of hip fracture



Cooper. Am J Med 1997; 103(2A):12s-19s.

Prognosis of Hip Fractures



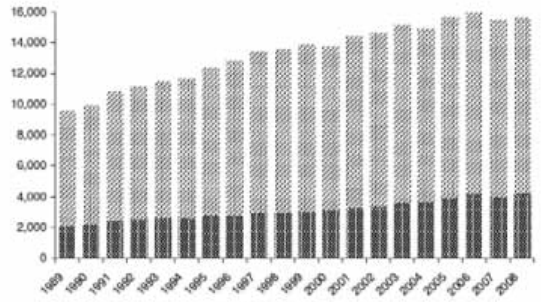


Fig. 1 Number of annual hip fracture discharges in Austrian population aged >50

HP Dimai et al Osteopor Int 2010

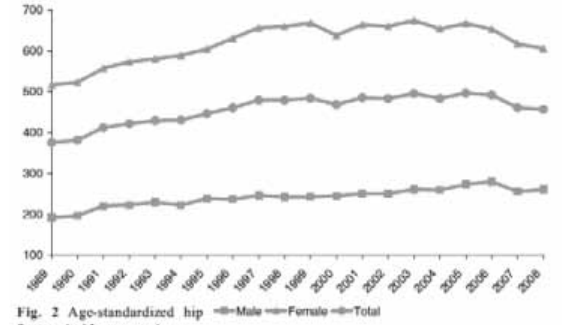


Fig. 2 Age-standardized hip fracture incidence rates (per 100,000) for the Austrian population aged ≥50

HP Dimai et al Osteopor Int 2010

What is osteoporosis ?

Disease vs. Definition

Disease vs. Consequences (Fractures)

What is osteoporosis ?

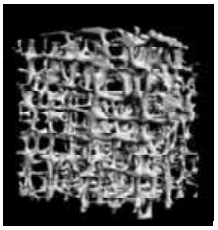
Patient, female 60a, severe osteoporosis

Osteoporosis

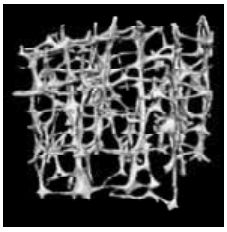
The clinical endpoint is the low energy (low trauma) fracture.

Most frequent osteoporotic fractures

This is osteoporosis.



Healthy Woman
52 yrs



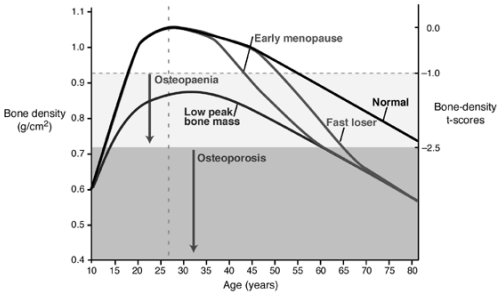
Woman with manifest osteoporosis 82 yrs

Borah, et al. Anat. Rec. 2001

Bone mass

Bone mineral density (BMD)

Bone Mineral Density



Diagnosis of Osteoporosis

BMD

D(E)XA

Definition of Osteoporosis

WHO Definition (t-scores)

BMD > -1.0	Normal
BMD -1.0 - -2.5	Osteopenia
BMD < - 2.5	Osteoporosis

Definition of Osteoporosis

Osteoporosis is a skeletal disease characterized by **low bone mass** and a **deteriorated micro-architecture** of bone which
increases the fragility of the bone and **increases the risk of fracture**.

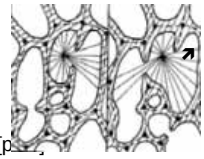
Kanis J et al JBMR 1994

Parameters of microarchitecture

Bone mass:
Proportion of bone volume and bone tissue

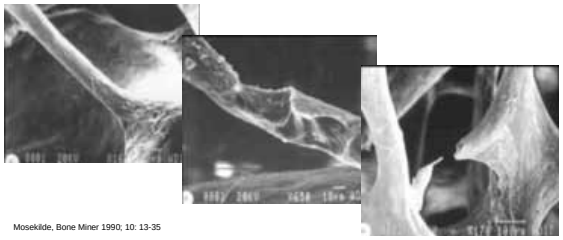
Structural elements:
Trabecular number
Trabecular thickness

Structural parameters:
Porosity (Marrow Star Volume) [p...]
Trabecular separation
Trabecular connectivity



Borah et al. Anat Rec 2002; 265 (2): 101-10

Loss of structures of horizontal trabeculae



Mosekilde, Bone Miner 1990; 10: 13-35

Importance of Horizontal Trabeculae

Structure 1 **Structure 2**

Assume: Volume 1 = Volume 2
Identical material and dimensions for both

Structure 1 is 16 x stronger than Structure 2

The Stability of Bone

depends not only on **Bone Mass (Bone Density)**,

but on Microarchitecture, too

(**Bone Quality**).

Bone Strength

Bone Quantity	**Bone Quality**
Bone mass	Macroarchitecure
Bone density	Microarchitecture
Size of bones	Bone turnover
	Bone formation
	Bone resorption
	Material properties
	Mineralisation
	Microfractures
	Collagen

NIH Consensus Development Panel

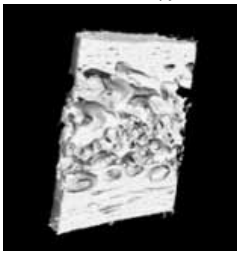
(JAMA 2001;285:785-95)

Osteoporosis is definded as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture.
Bone strength primarily reflects the integration of bone density and bone quality.

Osteoporosis Treatment

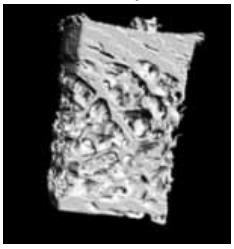
in premenopausal women

Before Therapy



Borah et al. OI 2002

After 1 year



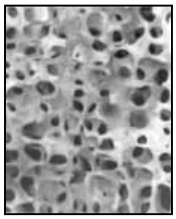
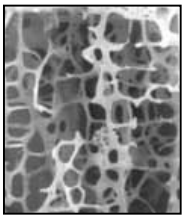
µCT Scanco

Increase in BMD does not correlate with Fractue Reduction

Studies	**Δ BMD (%)** vs. Placebo	**% Reduction** vert. Fracture risk
Calcitonin (PROOF) (Chestnut et al.)	0.5	36
Raloxifene (MORE) (Ettinger et al.)	2.6	40
Alendronate (FIT 1) (Black et al.)	6.2	47
Risedronate (Vert-MN) (Reginster et al.)	6.3	49
Fluorides (Favos 2y) (Meunier et al.)	8.4	no diff. to placebo
Teriparatide (Fract.Prev.Trial) (Neer et al.)	14.2	65
Srontiumranelate (TROPOS) (Meunier et al.	12.7 (Strontium effect)	41
Ibandronate (Meunier et al.	5.7 (interm.)	50

The amount of increase in BMD can only explain 4% up to 28% in fracture reduction (Watts et al., Sarkar et al., Cummings et al.)

Definition, Diagnosis and Treatment of Osteoporosis

Bone Strength - Bone Architecture

Wolff's law

Mechanical loads can affect bone architecture in living beings.

Julius Wolff
Das Gesetz der Transformation der Knochen
Berlin, A. Hirschwald
1892

What is osteoporosis ?

Osteoporosis is a risk factor for fractures.
Michael McClung 2007



What is a Fracture ?

A fracture is a

complete disruption of a bone,

occuring after
high-impact trauma,
over-loading,
low impact trauma in an abnormal or pathological bone.

Types of Fracture

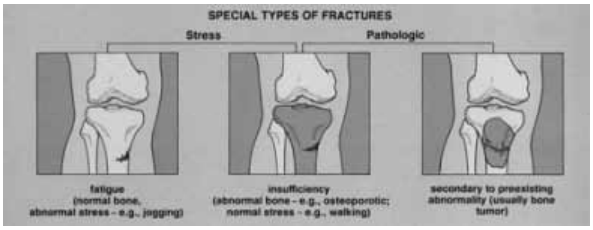
High-impact trauma fracture

Overloading – **Stress fracture**

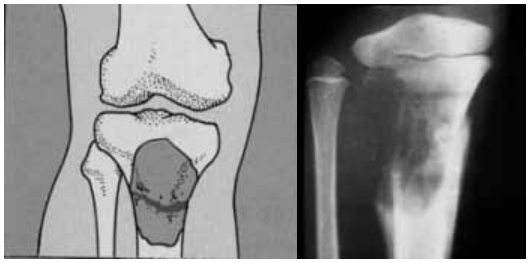
Fracture in pathological bone tissue - **Insufficiency fracture**

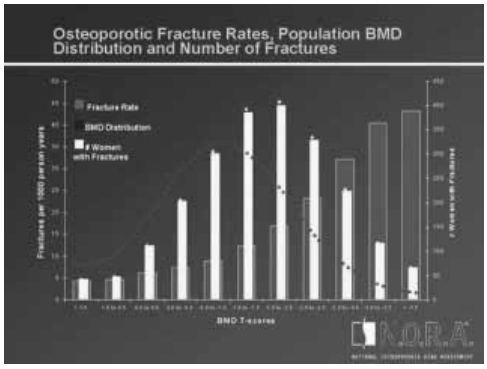
Osteolysis – **Pathological Fracture**

High-impact Trauma fracture



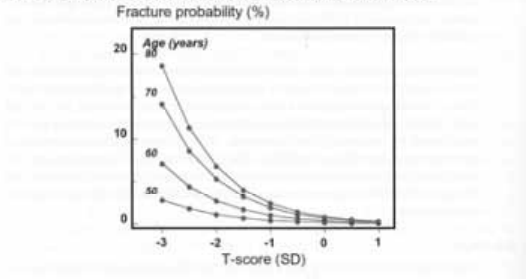
Pathological Fractures





Source: Siris ES, et al. Surgeon General s Workshop on Osteoporosis 2002. *J Bone Miner Res* 2001; 16:Suppl 1, S337.

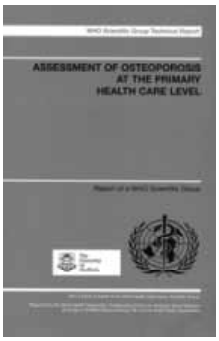
Fig. 5.1
The relationship between bone mineral density at the femoral neck expressed as a T-score and 10-year hip fracture probability in women from Sweden according to age



RISK Factors in WHO Predictive Model

Age
Sex
Femoral neck BMD
Prior fragility fracture after age 50 [1]
Body mass index
Ever use of corticoids
Secondary osteoporosis (e.g.; rheumatoid arthritis)
Parental history of hip fracture
Current cigarette smoking
Alcohol intake > 2 units / day

[1] hip, spine, distal forearm, proximal humerus, pelvis, ribs, proximal tibia in women



FRAX™ WHO Fracture Risk Assessment Tool

John A. Kanis

WHO Collaborating Centre for Metabolic Bone Diseases, Sheffield 2007

FRAX™

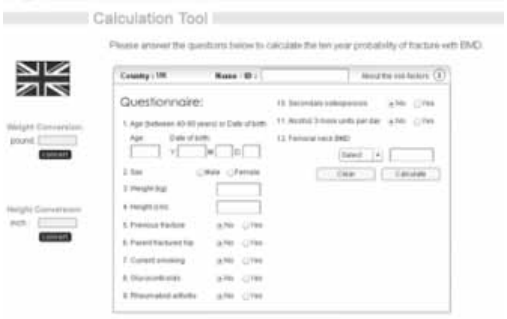
WHO Fracture Risk Assessment Tool

New WHO Recommandations

Absolute Fracture Risk Probability for 10 yrs

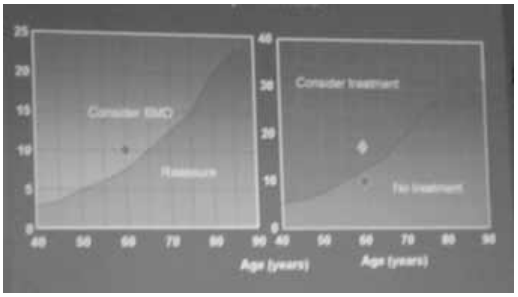
Case finding

Based not only on BMD

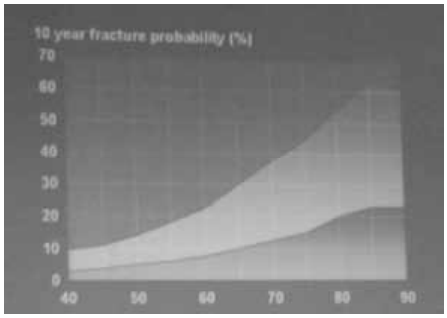


Assessment and Intervention Threshold Europe

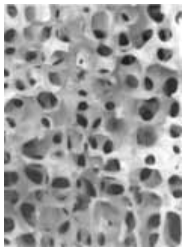
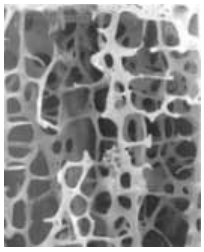
-Major Fracture –



Assessment threshold - Major Fracture



What is Osteoporosis ?

Cortical vs. Trabecular Bone

Cortical Bone

diaphyseal
bending load
low biological activity

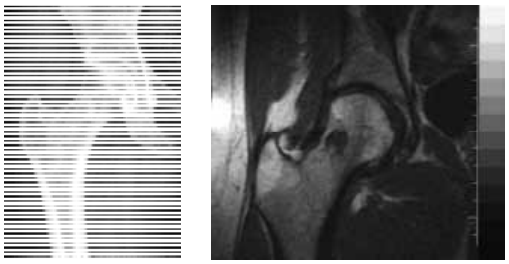
Trabecular Bone

meta / epiphyseal
pressure load
high biological activity

Cort. vs. Trabec. Bone fem. neck

Whole Bone	Cortex	Trabecular
Total Area: 632	Total Area: 218	Total Area: 414
	Percentage (%): 34.5 %	Percentage (%): 65.5 %

Background: Benigne Bone Tumors



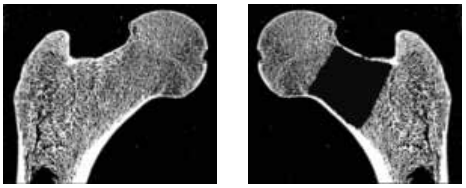
Pat. J.M., 45a, Fibrous Dysplasia (Cyst) fem. neck right

Idea of Study

Prepare paired proximal femurs with one normal femur (both cortical and trabecular bone) and the other with trabecular bone removed.

Test bone strength in both biomechanically.

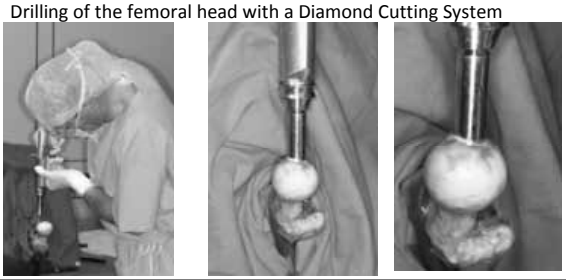
Model to test Hypothesis



Randomized excavation of trabecular bone of one bone of a pair.

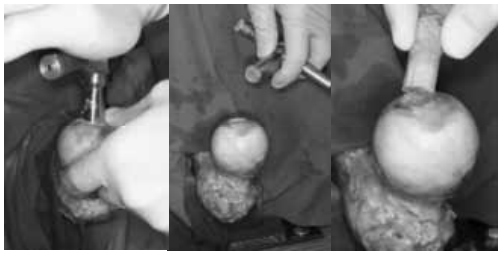
Preparation of Bones

Drilling of the femoral head with a Diamond Cutting System



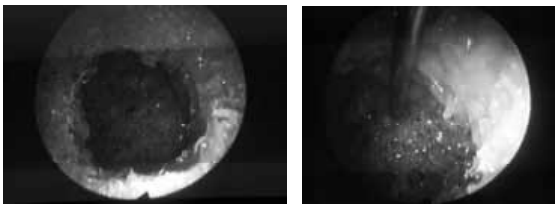
Preparation of Bones

Diamond Cutting System 15.25 mm + Removal of cylinders



Preparation of Bones

Excavation of the femoral neck by the use of a curette (randomized one bone of a pair)



Preparation of Bones

Placing the arthroscopic light source into the head of the femur

Full neck: head lighted

Excavated: neck lighted

Preparation of Bones

Replacing drilling cylinder into canal fixed with bone cement

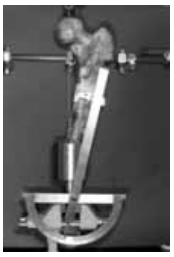
After Preparation of Bones

Biomechanical Testing

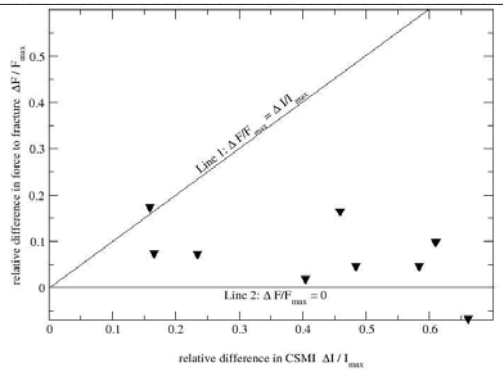
Tested for loading capacities (**forces to fracture**)

MTS
Mechanical
Testing
Systems

Eden Prairie
MN USA



Cross Sectional Area Speciman No 20



Experiment „Spongicort“

Results

Differences between forces needed to fracture excavated and intact femurs (ΔF / F mean):

mean: 7.0 % (range: 4,6 – 17,3 %).

Fracture load (ΔF / F mean) did not correlate with CSA of spongiosa removed nor did BMD.

Hip Fractures and the Contribution of Cortical Versus Trabecular Bone to Femoral Neck Strength

Gerold Holzer
Gobert von Skrbensky
Lukas A Holzer
Wolfgang Pichl

Journal of Bone and Mineral Research
March 2009: 24:468-474

Osteoporose neu untersuchen

Studie. Füllmaterial im Knochen möglicherweise für Festigkeit nicht entscheidend.

NZZ Online

Mittwoch, 18. Februar 2009, 20:23:57 Uhr, NZZ Online

Nachrichten > Forschung und Technik

18. Februar 2009, Neue Zürcher Zeitung

Umdenken bei der Osteoporose

Ein Experiment zur Frage, was den Knochen bruchfest macht

Bei der Osteoporose werde zu stark auf die Knochenbälkchen im Innern des Knochens fokussiert, sagt ein Wiener Mediziner. Warum das falsch sei, demonstriert er an Knochen von Leichen.

ni. Auf der Online-Plattform des «Journal of Bone and Mineral Research» ist die Studie des Orthopäden Gerold Holzer und seiner Mitstreiter von der Universität Wien schon im November erschienen. Dass die Arbeit damals an der Öffentlichkeit vorbeiging, dürfte daran liegen, dass die Fachzeitschrift nur von Knochenspezialisten gelesen wird. Vom Inhalt her ist die fehlende Aufmerksamkeit jedenfalls nicht zu erklären, denn die Studie ist brisant. Holzers Gruppe will mit ihrer im März auch in gedruckter Form vorliegenden Untersuchung mit einer alten Vorstellung aufräumen: Die Stärke des Knochens, so der Tenor der Arbeit, hänge entgegen der verbreiteten Meinung praktisch nicht von den Knochenbälkchen im Innern des Knochens (Spongiosa), sondern fast ausschliesslich von der äusseren Knochenschicht (Corticalis) ab.[1]

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HIDDEN JEWELS | Diabetes & Endocrinology | calculated on 17 September 2009

The "Hidden Jewels" Top 10 lists are generated every day and comprise only articles published in less widely distributed journals. The articles are ordered by the number of times an article's evaluation(s) has/have been viewed over the past 30 days. The general journals and specialty journals excluded from this list are: *Acta Arch Intern Med, Ann Intern Med, ANN, Cell, CMAJ, Endocrinology, Field Stock, J Clin Endocrinol Metab, J Clin Invest, JAMA, Lancet, N Engl J Med, Nat Med, Nature, Science.*

Hip fractures and the contribution of cortical versus trabecular bone to femoral neck strength.
Holzer G, von Skrbensky G, Holzer LA, Pichl W
J Bone Miner Res 2009 Mar **24**(3):468-74
[abstract on PubMed] [related articles] [full text] [order article]

Die Knochendichte selbst ist jedoch nur zum Teil für das erhöhte Bruchrisiko der Knochen bei Osteoporose verantwortlich; die Bruchfestigkeit wird im Wesentlichen von der äußeren Compacta-Schicht bestimmt, während die Knochendichtemessung vor allem auch den trabekulären Knochen misst.[4]

Holzer, G. et al.: Hip fractures and the contribution of cortical versus trabecular bone to femoral neck strength. J Bone Miner Res. 2009 Mar;24(3):468-74.

Conclusion

Trabecular bone in respect to bone strength plays just a marginal role.

Difference between full and excavated bone (ΔF / F mean): 7.0 %

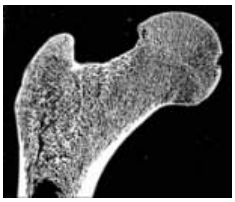
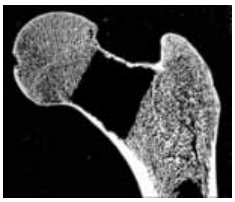
Mostly responsible for bone strength:

Cortical bone

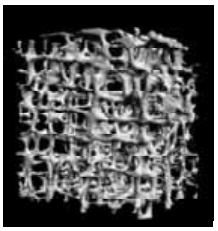
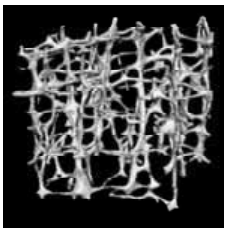
Consequences

Questions:

What is the importance of trabecular bone for fracture risk, when the contribution to bone strength is only marginal ?

What does osteoporosis has to do with fractures ?

Healthy Woman
52 yrs

Woman with osteoporosis
82 yrs

Borah, et al. Anat. Rec. 2001

WHO Definition of Osteoporosis Diagnosis

BMD > -1.0	Normal
BMD -1.0 - -2.5	Osteopenia
BMD < - 2.5	Osteoporosis

Is this still relevant when cortical bone counts for most of bone strength ?

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is cortical. Most skeletal bone mass is cortical, not trabecular. In vertebrae, the amount of cortical bone has been estimated at 30–60%, but 45–75% of the axial load on a vertebral body is borne by cortical bone.[1] In the femoral neck, the cortical shell contributes 40–90% of the bending rigidity.[1] In laboratory studies, removal of trabecular bone from the femoral neck only reduced fracture load by 7%, suggesting that an intact cortex was important for failure prevention.[1] Any increase in cortical porosity will compromise load-bearing capacity.

Situation now

1. **Drugs that work**
   shown in larger studies
   reduce bone fragility and number of fractures
2. **Poor surrogate parameter**

Increase in BMD does not correlate with Fracture Reduction

Studies	Δ BMD (%) vs. Placebo	% Reduction vert. Fracture risk
Calcitonin (PROOF) (Chestnut et al.)	0.5	36
Raloxifene (MORE) (Ettinger et al.)	2.6	40
Alendronate (FIT 1) (Black et al.)	6.2	47
Risedronate (Vert-MN) (Reginster et al.)	6.3	49
Fluorides (Favos 2y) (Meunier et al.)	8.4	no diff. to placebo
Teriparatide (Fract.Prev.Trial) (Neer et al.)	14.2	65
Srontiumranelate (TROPOS) (Meunier et al.	12.7 (Strontium effect)	41
Ibandronate (Meunier et al.	5.7 (interm.)	50

The amount of increase in BMD can only explain 4% up to 28% in fracture reduction (Watts et al., Sarkar et al., Cummings et al.)

What is the morphological basis of Bone Fragility ?

- 80% of bone is cortical.
- Cortical bone loss is the most important issue of bone fragility.
- 70% of bone loss is due to intracortical porosity.

Seeman 2011

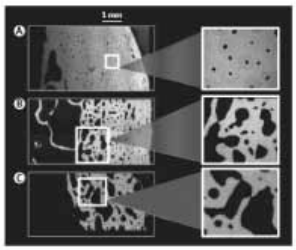
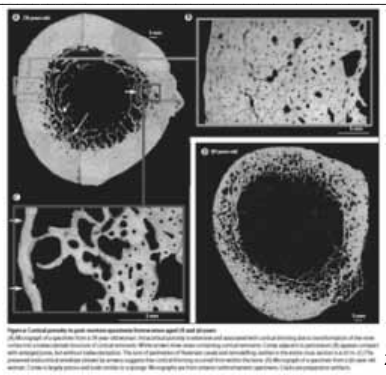


Figure 3: Porosity in post-mortem specimens from three women of different ages
(A) Micrograph of a specimen from a 29-year-old woman. Pores are regular in shape and evenly distributed in the cortex. (B) Micrograph of a specimen from a 67-year-old woman. Pores are large, irregularly shaped, and have coalesced in cortex adjacent to the marrow (producing cortical remnants). (C) Micrograph of a specimen from a 93-year-old woman. Most of the cortex is trabecularised by large and coalesced pores. Micrographs are of anterior subtrochanteric specimens.

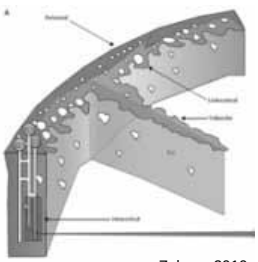
Zebaze 2010



Zebaze 2010

Bone has surfaces.

- periostal surface
- endocortical surface
- intracortical surface
- trabecular surface

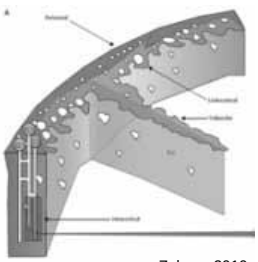


Zebaze 2010

Bone has surfaces.

Activity on these surfaces
(Life on bone)

Cells

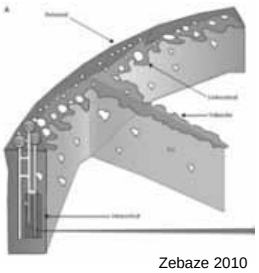


Zebaze 2010

Bone has surfaces.

How can we measure

these surfaces ?



Zebaze 2010

Bone Qualities

- different qualities
- What qualities are bone made of in order to define bone fragility ?
- How measure bone fragility ?

Seeman 2011

Requirements for Surrogate Parameter

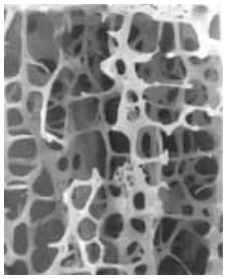
Non-invasive, non-destructive
Good correlation with bone fragility (fractures)
Simple to do
Widely available
No (low) radiation

Eiffel Tower – Trabecular – Cortical ?

Eiffel Tower – Trabecular – Cortical ?

Bones are tubes, no Eiffel towers.

Osteoporosis vs. Fractures



Osteoporosis – Fracture Disease

is the consequence of a stochastic process, that is multiple genetic, physical, hormonal and nutritional factors acting alone or in a concert to diminish skeletal integrity.

Robert Marcus 1996

conflict and confuse--冲突和困惑

	Research concern 医生关注	PTs. Need 患者关注
Total	25804	147/441
fracture	22.45%	17.01%
calcium	17.69	34.69
vitamin D	0.095	9.52
pain	0.06	*76.87
death	0.03	4.76
balance	0.02	2.04
Muscle strength	0.005	*40.14
QOL	0.002	*42.18
sensory lose	<0.001	21.09
ADL	<0.001	*51.70

The center of attention.

Thanks for your attention !

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