In-Vivo Bone Mineral Density and Structures in Humans: From Isotom Over Densiscan to Xtreme-CT

Maximilian A. Dambacher (✉) , Maurus Neff, Helmut R. Radspieler, Peter Rüegsegger, and Ling Qin

Zurich Osteoporosis Research Group (Zurich-Munich-Hong Kong)
e-mail: m.dambacher@bluewin.ch

Brief History of Device Development and Related Studies

In the early 1960s, Prof. Rüegsegger, Institute for Medical Technology and Medical Informatics, Eidg. Technische Hochschule (ETH) and University in Zurich, was asked by the NASA to develop a device cable of quantifying bone loss in astronauts and people working or training under conditions of weightlessness (micro-gravity).

The result was the Isotom, a small tomograph for peripheral quantitative computed tomography (pQCT), which allowed us in these early days to perform measurements of the trabecular compartment of the bone only, as the cortical part of the bone was not yet accessible (Fig. 1; Rüegsegger et al. 1976, 1981). Our first step was to perform "bed-rest studies" in male volunteers in 1969. After 15 weeks of immobilization, trabecular bone loss exceeded 15% in the radius, a tremendously high bone loss as compared with the approximately 1% of yearly trabecular bone loss in perimenopausal women.

Having completed these studies, the device was transferred back to Zurich and we decided to adapt it in order to match the specific needs of our patients with osteoporosis. This laid the basis for Generation 2, i. e. the Densiscan 1000, manufactured by

Figure 1. Generation 1, Isotom (pQCT)

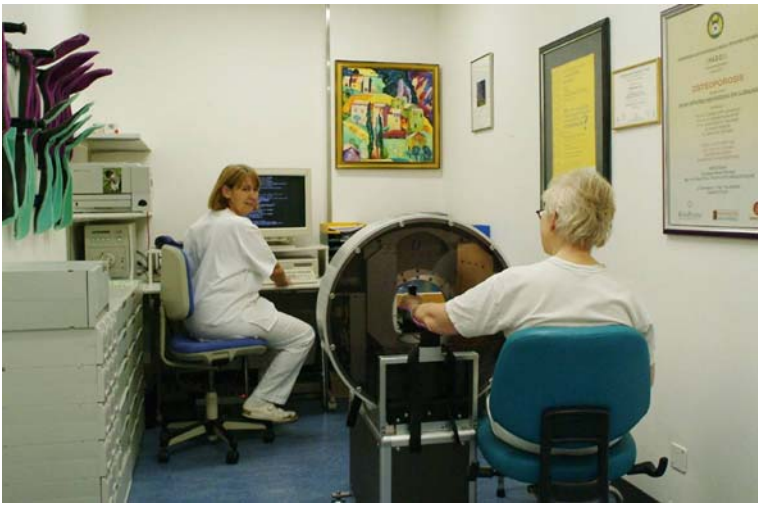


Figure 2. Generation 2, Densiscan 1000 (pQCT)

Scanco Medical AG in Bassersdorf/Zurich, Switzerland (Fig. 2). The key characteristics include separate measurement of trabecular and cortical bone in vivo at a lateral resolution of 0.2 mm. The default measurement program includes 16 tomograms in total at both distal radius and tibia (Fig. 3).

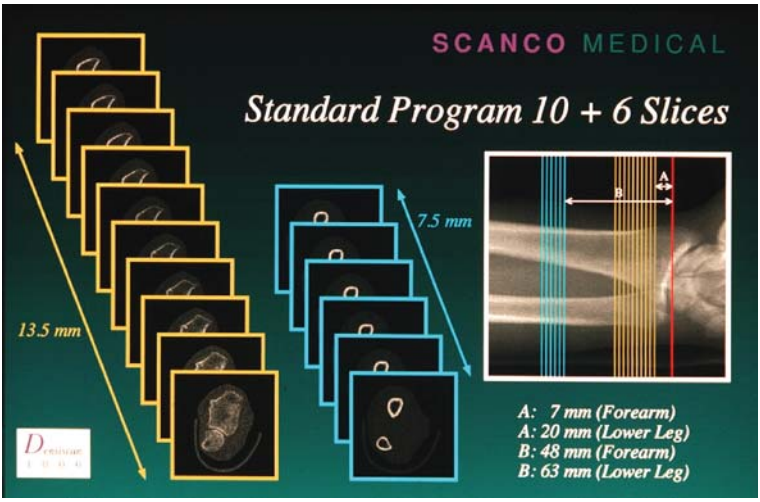


Figure 3. Real imaging of multilayer pQCT (Densiscan 1000) with standard measurement program with ten tomograms for the ultradistal radius and six tomograms for the distal radial midshaft

Strength of the Device Generation 2 in Research and Clinical Evaluations

By the end of 2005, we delivered 150 in vitro and in vivo devices from our Densiscan Series to worldwide leading research organizations. With the Densiscan System, now we are working on the five typical research areas or questions given herein, among others.

Separate Evaluation of Cortical and Metabolically More Active Trabecular Bone

Do the trabecular and the cortical compartments of bone belong to one and the same system, responding to identical rules and factors, or do they differ, eventually even showing differences in bone dynamics? The answer is "Yes".

In perimenopausal women, cortical bone was found to remain relatively stable, but trabecular bone underwent a marked loss, reaching up to 5% over these 20 months of observation (Fig. 4; Rüegsegger et al. 1981). A similar phenomenon was observed over 12 months in tetra- and paraplegics, in the radius as well as the tibia, whereby trabecular bone loss was shown to be far more pronounced than cortical bone loss (Frey-Rindova et al. 2000; de Bruin et al. 1999, 2000, 2005). Fast rate of bone loss in trabecular bone as compared with that of cortical bone found in Caucasian women (Dambacher 1999a,b, 2001a) was also shown in studies from Asian population (Ito et al. 1998; Qin et al. 2000, 2002a, 2003a,b).

Because of the differences in rate of bone loss between cortical and trabecular bone, pQCT was used to explore the exercises in prevention of bone loss in postmenopausal women, such as the studies related to the Chinese martial art Tai Chi Chuan, where significant preventive effects were demonstrable more in trabecular bone (Qin et al. 2002b, 2003a,b, 2005; Chan et al. 2004). The pQCT also showed its

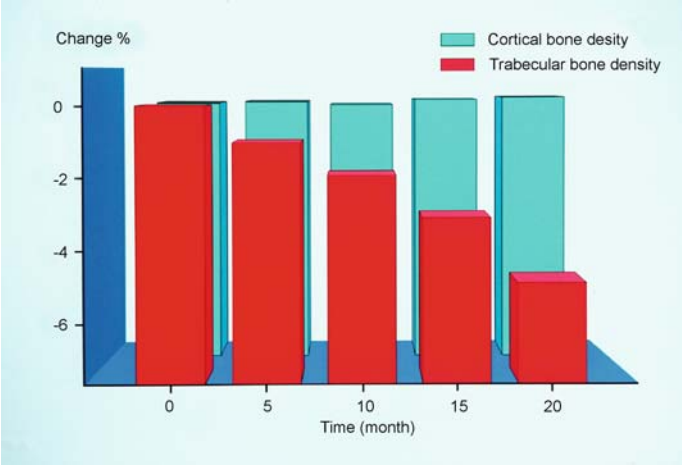


Figure 4. Perimenopausal trabecular and cortical bone loss over 20 months of observation

advantages in detecting inactivity-induced bone loss, such as changes of bone mineral status in weight-bearing tibia bone properties after spinal cord injury (de Bruin et al. 1999, 2000, 2005).

Regional Variations in Bone Mineral Density and Structure

As our pQCT is a 3D technique, its advantage to 2D techniques is seen in its recent applications in studying regional variations in volumetric BMD in perpendicular skeletons in conjunction with biomechanical evaluations of weight-bearing or loading effects (Lai et al. 2005a,b).

pQCT Measurement at Perpendicular Skeletons and its Relationship with Central or Axial Devices

It was repeatedly alleged, thereby reflecting the knowledge gaps, that peripheral measurements would not be representative for the lumbar spine. Ito et al. (1998, 1999) performed longitudinal and cross-sectional examinations with our device and showed a highly significant correlation between axial and peripheral measurements, *when comparing what should be compared*, i. e. trabcular bone with trabecular bone. Similar conclusions applied to the dynamics of trabecular bone loss were drawn in Ito et al.'s study with a follow-up of up to 5 years after menopause (Fig. 5; Ito et al. 1998).

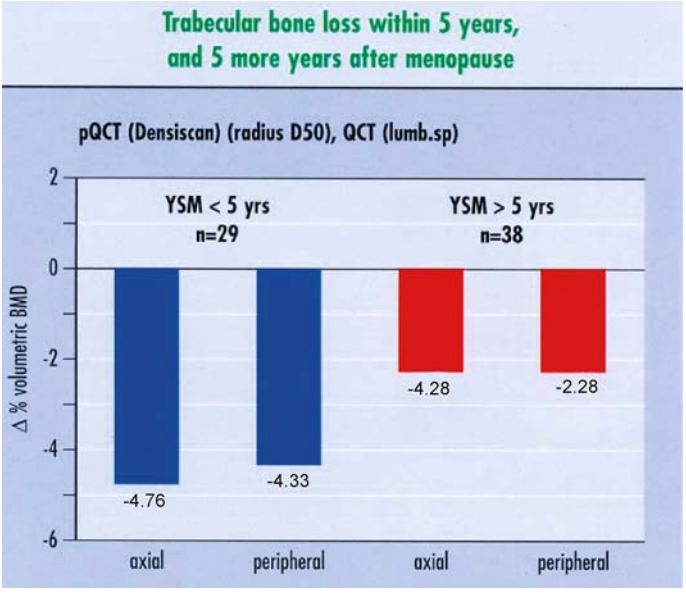


Figure 5. Similar rate of bone loss in trabecular bone compared between axial QCT and pQCT in both pre- and postmenopausal women

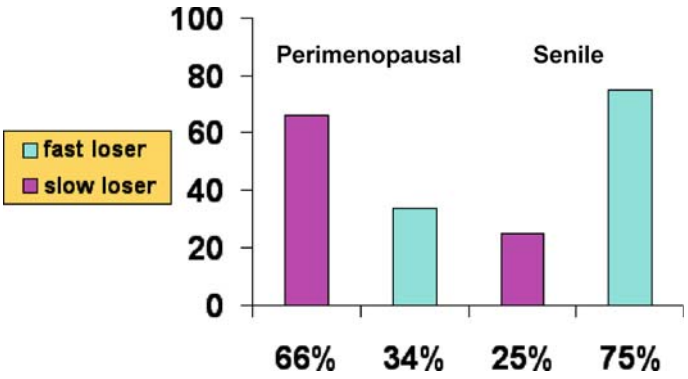


Figure 6. Distribution of fast and slow loser in perimenopausal and severely osteoporotic (senile) patients. Rate of bone loss is based on the rate of trabecular bone loss at non-dominant distal radius

Types of Osteoporosis and Rate of Bone Loss

The individualization of osteoporosis into two distinct types, type I and type II, is still actual, whereby rapid bone loss is referred to as type-I osteoporosis, and type-II osteoporosis would apply to stable bone dynamics or to a slow rate of bone loss. To differentiate between rapid and slow rates of loss of bone substance, we categorized our patients into "fast" and "slow" losers, reflecting the bimodal distribution of the rates of trabecular bone loss in women aged between 45 and 55 years, whereby patients defined as "fast losers" lost more than 3.5% of trabecular BMC per year (Dambacher et al. 1998; Rüegsegger et al. 1996; Qin et al. 2003a,b).

During perimenopause, 34% of our patients only showed a "fast bone loss", and the remaining 66% had a normal rate of loss in volumetric bone density (Fig. 6). This is consistent with the observation that only one of three women will effectively develop osteoporosis and therefore become eligible for treatment. During those days, we were accused of "acting like rebels", as we disagreed with the dogma which required that every post-menopausal woman underwent estrogen replacement therapy. In contrast, the proportion of "fast losers" reached 75% in patients with severe (senile) osteoporosis (type II). This contradicts common current scientific knowledge, a contradiction which can be explained by the fact that trabecular bone is not examined independently but only in combination with cortical bone, although these two bone compartments act as totally different systems with distinct dynamics. Another problem arises from the presentation of rates of bone loss in relative and not absolute values.

Reproducibility and Pitfalls of Devices

Long-Term Reproducibility

The long-term reproducibility is a relative measure of the precision of repeated measurements over a more or less prolonged period of time. Reproducibility depends

Table 1. Reproducibility and the required time frame between two measurements for evaluation of "fast bone losers" (at 95% confidence level)

	Multi-layer pQCT				DXA (%)			QUS (%)			
Precision error	±0.3	±0.5	±1.0	±1.5	±2.0	±2.5	±3.0	±3.5	±4.0	±4.5	±5.0
Minimal time	***3***	***5***	***9***	***14***	***19***	***24***	28	33	38	42	47
interval	***3***	***5***	***10***	***15***	***21***	26	31	36	41	46	51
between two	***3***	***6***	***11***	***17***	***23***	28	34	40	45	51	57
repeated	***4***	***6***	***13***	***19***	25	31	38	44	50	57	63
measurements	***4***	***7***	***14***	***21***	28	35	42	50	57	64	71
(months)	***5***	***8***	***16***	***24***	32	40	49	57	65	73	81
	6	***9***	***19***	28	38	47	57	66	75	85	94
	7	***11***	***23***	34	45	57	68	79	91	102	113
	8	***14***	28	42	57	71	85	99	113	127	142

Data highlighted in italics and boldface: measurement interval < 2 years and the rest refers to measurement interval > 2 years

on the method used and the value of bone density at baseline. Table 1 shows the level of reproducibility required to be able to identify a fast loser patient within a given time frame. With the high-resolution pQCT measurement method and assuming a baseline bone density value of 50% and a reproducibility of 0.3%, 7 months would be required to identify a fast-loser patient (Dambacher et al. 1998; Qin et al. 2002a, 2003a,b). When using a routine DXA method for bone density measurement, with a reproducibility of 1–2%, this time frame increases to more than 24 months (Rüegsegger 1996). In this regard, the following statement from Delmas (1999) is of interest: "In patients with osteoporosis and with high bone turnover (fast loser condition) antiresorptive agents like Bisphosphonates, SERMS and calcitonin should be used. In patients with low bone turnover (slow loser condition) fluorides should be applied, regardless of the discussion about fluorid medication".

Pitfalls

The pitfalls or limitations of the above-mentioned device are found in either "false-positive" or "false-negative" conditions, including measurement sites with microfractures (misinterpreted as an increase in BMD) or with healing of microfractures (misinterpreted as a "fast-loser" status (Figs. 7a-c).

The Latest Development: Generation 3, Xtreme-CT for In-Vivo Human Studies

Rationale of Device Development

On 22 September 2003, in Minneapolis, Harry Genant organized a symposium entitled "Beyond". In his mind, the measurement of bone density in humans alone was

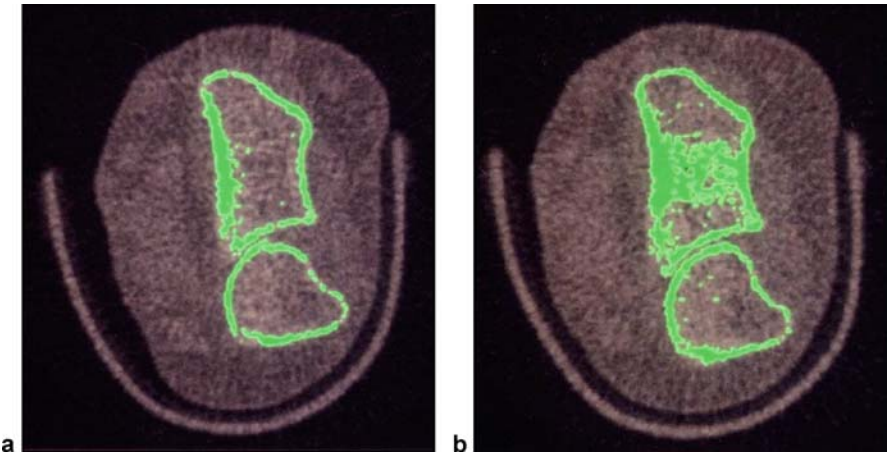


Figure 7. Microfracture results in "false-positive" results in BMD values. **a** At the time of fracture at distal radius. **b** A few months after fracture, with increased trabecular BMD in the central part of the distal radius on the pQCT image, i. e. formation of micro-fracture

to be considered as insufficient. In fact, all proposed definitions or consensus statements of osteoporosis (Copenhagen 1990, Hong Kong 1993, Amsterdam 1996 and the Consensus Development Conference 2001) do highlight the importance of bone structure. During the past years, it has become increasingly clear that an increase in BMD is not accompanied by a parallel decrease of fracture risk. Table 2 shows very

Table 2. The increase in BMD does not correlate with the decrease in fracture risk

Fracture end-point studies	Difference in BMD as compared with placebo (%)	Reduction of vertebral fractures (%)
Calcitonine (PROOF) (Chestnut et al. 1993)	0.5	36
Raloxifene (MORE) (Ettinger et al. 1999)	2.6	40
Alendronate (FIT 1) (Black et al. 1999)	6.2	47
Risedronate (Reginster et al. 2000)	6.3	49
Fluoride (Meunier et al. 1998)	8.4	No difference
Teriparatide (Neer et al. 2001)	14.2	65
Strontium ranelate (Meunier et al. 2004)	12.7	41
Ibandronate (Recker et al. 2004)	5.7	50

Figure 8. Generation 3, Xtreme-CT

clearly that BMD is accountable for only 20% of the observed fracture risk reduction (Dambacher et al. 2004a,b).

Additionally, a poster was presented by Watts (2005), with the following title: "Risedronate demonstrates efficacy to reduce fragility fractures independent of treatment related BMD changes". Moreover, at 2005 ASBMR Pierre Delmas stated: "Half of incident fractures occur in osteopenic women who have BMD values above the WHO defined diagnostic threshold for osteoporosis". Similar thoughts triggered us, much earlier, to go ahead with the development of the Generation 3 of our device, i. e. Xtreme-CT, for the representation and the quantitative measurement of 3D structures in vivo in humans (Figs. 8, 9; Dambacher et al. 2001b, 2004a,b; Neff et al. 2002). This device features a reproducibility of total, trabecular and cortical BMD of 0.7–1.5% and of 2.5–4.4% for trabecular architecture (P. Delmas, pers. commun.), with a resolution of 100 µm.

The Specific Features of In-Vivo Human Xtreme-CT

The recent application of this latest development suggests that Xtreme-CT may have the following characteristics:

1. Its ability to discriminate between osteopenic women with and without a prior history of fracture. In contrast, spine and hip BMD measured by DXA were not different between the two groups (P. Delmas, pers. commun.).
2. Its quantitative assessment of trabecular microarchitecture (Figs. 10–12) allows an improved assessment of fracture risk.

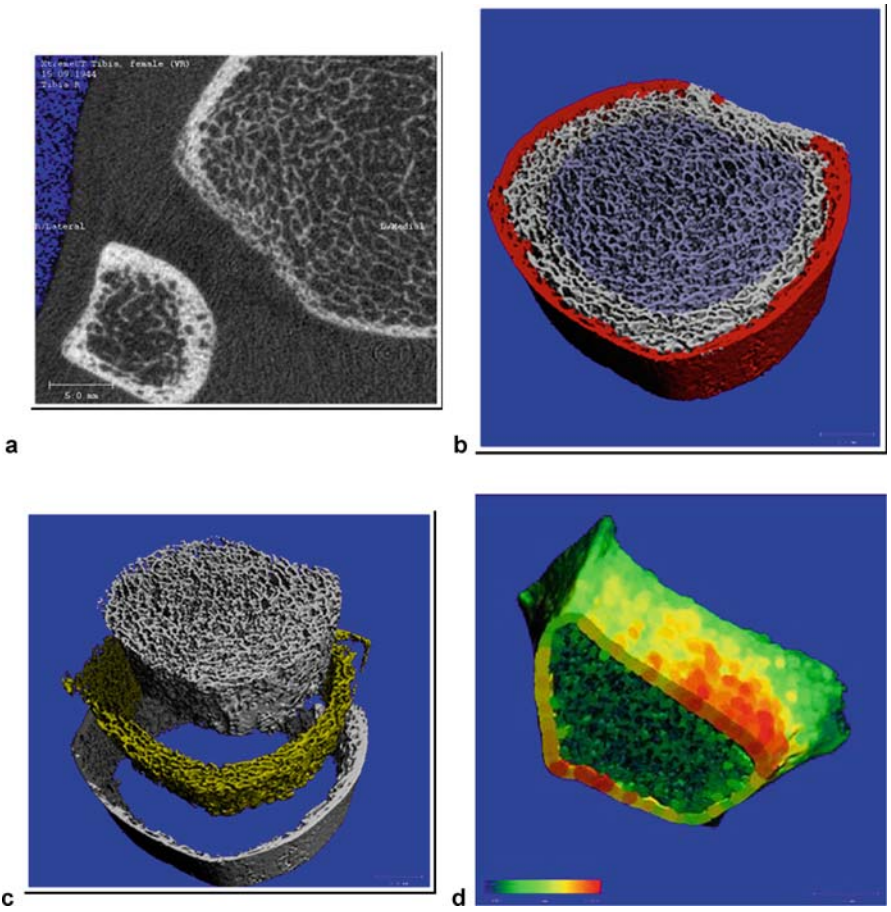


Figure 9. In-vivo Xtreme-CT for human application with 3D reconstructions. **a** A 2D image of ultradistal radius. **b** A 3D reconstruction with defined region of interests. **c** A "cut out" of region of interests defined in **b**. **d** A 3D reconstruction of radial cortical shell at distal radial diaphysis

3. Better monitoring of treatment effects (Fig. 13).
4. It allows prospective studies to assess osteopenic patients at increased risk for fracture.

The technical details of the above-mentioned devices are summarized on the homepage of the devices: http://www.scanco.ch.

Conclusion

The motivation for development of 3D bone densitometry was attributed to NASA space flight in early 1960s. Over the years, we have been able to advance our engi-

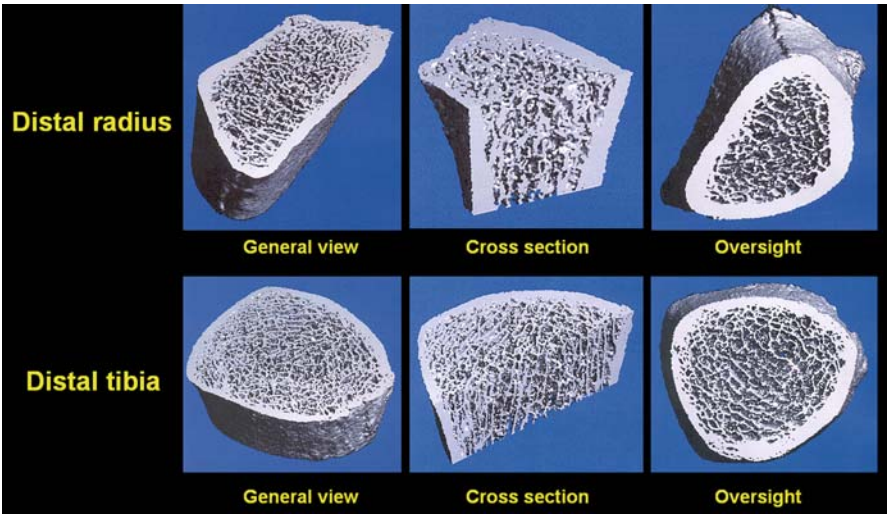


Figure 10. The Xtreme-CT: 3D structure presentations at various views of normal distal extremities

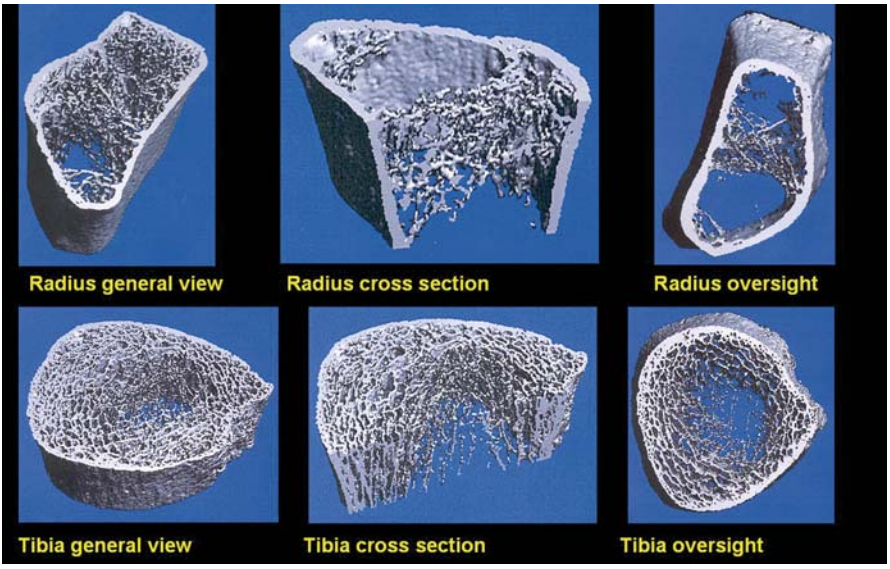


Figure 11. The Xtreme-CT: 3D structure presentations at various views of osteoporotic distal extremities

neering significantly, and our latest development in this area is the in vivo human Xtreme-CT, which enables us to measure and monitor the changes of 3D bone structures in vivo in humans. This opens a new horizon to evaluate the efficacy of the drugs developed for prevention and treatment of osteporosis, and potentially also for monitoring osteoporotic fracture repair.

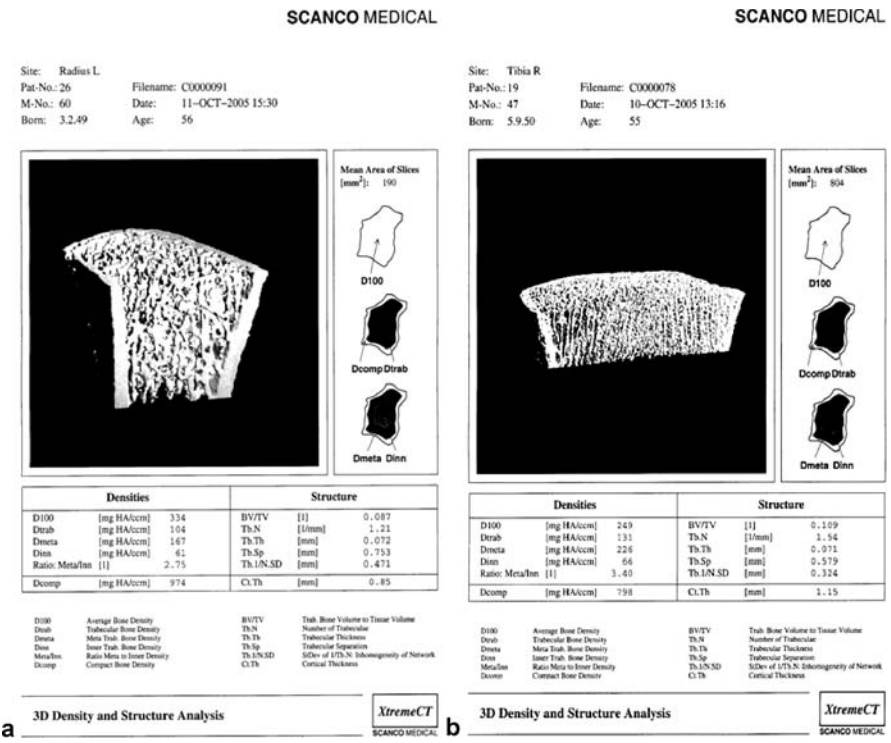
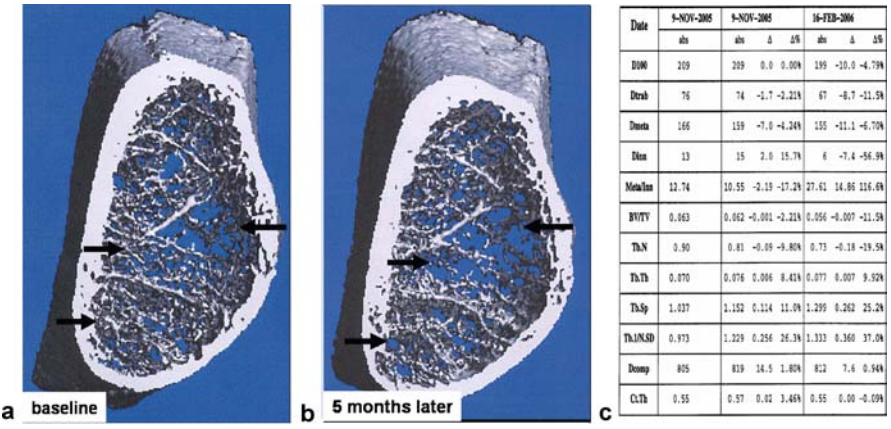


Figure 12. Datasheets of in vivo Xtreme-CT 3D reconstructions (corresponding to Figs. 10 and 11). **a** Datasheet of distal radius. **b** Datasheet of distal tibia



Date	9-NOV-2005	9-NOV-2005			16-FEB-2006		
	abs	abs	Δ	Δ%	abs	Δ	Δ%
D100	209	209	0.0	0.00%	199	-10.0	-4.79%
Dtrab	76	74	-1.7	-2.21%	67	-8.7	-11.5%
Dmeta	166	159	-7.0	-4.24%	155	-11.1	-6.70%
Dinn	13	15	2.0	15.7%	6	-7.4	-56.9%
Meta/Inn	12.74	10.55	-2.19	-17.2%	27.61	14.86	116.6%
BV/TV	0.063	0.062	-0.001	-2.21%	0.056	-0.007	-11.5%
Tb.N	0.90	0.81	-0.09	-9.80%	0.73	-0.18	-19.5%
Tb.Th	0.070	0.076	0.006	8.41%	0.077	0.007	9.92%
Tb.Sp	1.037	1.152	0.114	11.0%	1.295	0.262	25.2%
Tb.1/N.SD	0.973	1.229	0.256	26.3%	1.333	0.360	37.0%
Dcomp	805	819	14.5	1.80%	812	7.6	0.94%
Ct.Th	0.55	0.57	0.02	3.46%	0.55	0.00	-0.09%

Figure 13. The Xtreme-CT: monitoring of trabecular bone loss of at distal radius of a postmenopausal women. **a** A 3D distal radius at baseline (*arrows*). **b** A 3D distal radius of the same region made 5 months after baseline measurement (*arrows*: demonstrating trabecular bone structural deterioration and loss). **c** Datasheet for comparison of density and structural values

References

Black DM, Thompson DE (1999) The effect of alendronate therapy on osteoporotic fracture in the vertebral fracture arm of the Fracture Intervention Trial. Int Clin Practice 101:46–50

Chan KM, Qin L, Lau MC, Woo J, Au SK, Choy WY, Lee KM, Lee SH (2004) A randomized, prospective study of the Tai Chi Chun exercise on bone mineral density in postmenopausal women. Arch Phy Med Reha 85(5):717–722

Chestnut CH III (1993) Calcitonin in the prevention and treatment of osteoporosis. Osteoporosis Int 3 (Suppl 1):206–207

Dambacher MA, Neff M, Kissling R, Qin L (1998) Highly precise peripheral quantitative computed tomography for the evaluation of bone density, loss of bone density and structures. Drugs Aging 12:15–24

Dambacher MA, Neff M, Radspieler H, Qin L (1999a) Ist die herrschende Meinung "Perimenopausal schneller – Senile Osteoporose langsamer Knochenverlust" korrekt? J Menopause 6:10–11

Dambacher MA, Radspieler H, Neff M, Schacht E, Qin L., Kissling R (1999b) "Fast" und "slow-loser" Patienten: Eine sinnvolle Unterscheidung? Konsequenzen für die Praxis. ("Fast-" and "slow-loser" patients: A useful differentiation? Consequences for our daily practice). Osteologie 8:152–160

Dambacher MA, Neff M, Kissling R, Qin L (2001a) Das fast/slow bone loser Konzept. Osteopor Rheum Aktuelle 3:38–45

Dambacher MA, Neff M, Qin L, Rüegsegger P (2001b) 2- und 3-Dimensionale Knochenstrukturen in vivo und in vitro. J Miner Stoffwechsel 3:26–33

Dambacher MA, Schmitt S, Schacht E, Ito M, Neff M, Müller R, Qin L, Zhao YL (2004a) Bone structures in vitro and in vivo in animals and in men: a view into the future. J Miner Stoffwechs 11:13–19

Dambacher MA, Schmitt S, Schacht E, Ito M, Neff M, Müller R, Qin L, Zhao YL (2004b) Bone structures in vitro and in vivo in animals and in men: a view into the future. J Miner Stoffwechs 2:22–28

de Bruin ED, Frey-Rindova P, Herzog RE, Dietz V, Dambacher MA, Stussi E (1999) Changes of tibia bone properties after spinal cord injury: effects of early intervention. Arch Phys Med Rehab 80:214–220

de Bruin ED, Dietz V, Dambacher MA, Stussi E (2000) Longitudinal changes in bone in men with spinal cord injury. Clin Rehab 14:145–152

de Bruin ED, Vanwanseele B, Dambacher MA, Dietz V, Stussi E (2005) Long-term changes in the tibia and radius bone mineral density following spinal cord injury. Spinal Cord 3:96–101

Delmas P (1999) Presentation at the 1999 European Congress on calcified Tissue, Maastricht

Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Gluer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR (1999) Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. J Am Med Assoc 282:637–645

Frey-Rindova P, de Bruin ED, Stussi E, Dambacher MA, Dietz V (2000) Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography. Spinal Cord 38:26–32

Ito M (1998) Trabecular bone loss within 5 years and 5 years and more after menopause. Bone 23:S619

Ito M, Nakamura T, Tsurusaki K, Uetani M, Hayashi K (1999) Effects of menopause on age-dependent bone loss in the axial and appendicular skeletons in healthy Japanese women. Osteoporos Int 10:377–383

Lai YM, Qin L, Hung VWY, Chan KM (2005a) Regional differences in cortical bone mineral density in weight-bearing long bone shaft: a pQCT study. Bone 36:467–471

Lai YM, Qin L, Yeung HY, Lee KM, Chan KM (2005b) Regional differences in trabecular BMD and microarchitecture of weight bearing bone under habitual gait loading: a pQCT and microCT study in human subject. Bone 37:274–282

Meunier PJ, Sebert JL, Reginster JY, Briancon D, Appelboom T, Netter P, Loeb G, Rouillon A, Barry S, Evreux JC, Avouac B, Marchandise X (1998) Fluoride salts are no better at preventing new vertebral fractures than calcium-vitamin D in postmenopausal osteoporosis: the FAVO Study. Osteoporosis Int 8:4–12

Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, Cannata J, Balogh A, Lemmel EM, Pors-Nielsen S, Rizzoli R, Genant HK, Reginster JY (2004) The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 350:459–468

Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH (2001) Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344:1434–1441

Neff M, Dambacher MA, Kissling R, Qin L, Rüegsegger P (2002) Quantified 2- and 3-dimensional evaluation of bone structures in vitro and in vivo. Osteologie 11:67–77

Qin L, Au SK, Chan KM, Lau MC, Woo J, Dambacher MA, Leung PC (2000) Peripheral volumetric bone mineral density in pre- and postmenopausal Chinese women in Hong Kong. Calcif Tissue Int 67:29–36

Qin L, Au SK, Leung PC, Lau MC, Woo J, Choy WY, Hung WY, Dambacher MA, Leung KS (2002a) Baseline BMD and bone loss at distal radius measured by pQCT in peri- and postmenopausal Hong Kong Chinese women. Osteoporosis Int 13:962–970

Qin L, Au SZ, Choy YW, Leung PC, Neff M, Lee KM, Lau MC, Woo J, Chan KM (2002b) Regular Tai Chi exercise may retard bone loss in postmenopausal women: a case control study. Arch Phys Med Rehab 83:1355–1359

Qin L, Au SZ, Choy YW, Leung PC, Neff M, Lee KM, Lau MC, Woo J, Chan KM (2003a) Tai Chi Chuan and bone loss in postmenopausal women. Arch Phys Med Rehab 84:621–623

Qin L, Dambacher MA, Leung PC, Neff M (2003b) Fast and slow bone loss: diagnostic and therapeutic implications in osteoporosis. In: Schneider HPG (ed) Menopause the state of art: in research and management. Parthenon, New York, pp 124–130

Qin L, Choy WY, Leung KS, Leung PC, Au SK, Hung WY, Dambacher MA, Chan KM (2005) Beneficial effects of regular Tai Chi exercise on musculoskeletal system. J Bone Miner Metabol 23:186–190

Recker RR, Weinstein RS, Chesnut CH III, Schimmer RC, Mahoney P, Hughes C, Bonvoisin B, Meunier PJ (2004) Histomorphometric evaluation of daily and intermittent oral ibandronate in women with postmenopausal osteoporosis: results from the BONE study. Osteoporosis Int 15:231–237

Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, Lund B, Ethgen D, Pack S, Roumagnac I, Eastell R (2000) Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporosis Int 11:83–91

Rüegsegger P (1996) Bone density measurement. In: Bröll H, Dambacher MA (eds) Osteoporosis: a guide to diagnosis and treatment. Rheumatology 18:103–116

Rüegsegger P, Elsasser U, Anliker M, Gnehm H, Kind H, Prader A (1976) Quantification of bone mineralization using computed tomography. Radiology 121:93–97

Rüegsegger P, Anliker M, Dambacher MA (1981) Quantification of trabecular bone with low dose computed tomography. J Comput Assist Tomogr 5:384–390

Watts NB (2005) Risedronate demonstrates efficacy to reduce fragility fractures independent of treatment related BMD changes (poster). ASBMR, September, Nashville