OSTEOPOROSIS: WHERE DO WE STAND – WHERE ARE WE HEADING? DIAGNOSTIC POSSIBILITIES

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With the rising life expectation, the share of older people in the total population and thus the importance of osteoporosis, a disease that manifests itself with ageing, are also increasing continuously. In 1900, the life expectation of a newborn girl was less than 50 years; by 1997 it was 83 years. The number of women over the age of 65 will double by the year 2040. Today, osteoporosis is already the most common skeletal disorder. In about 25–30% of all women over the age of 60, it is so marked that deformations of the vertebral bodies are possible.

Osteoporosis has become an enormous socio-medical problem. Unfortunately, only about 20–30% of the "risk group" are currently diagnosed and receive prophylactic treatment. We will only be able to manage the osteoporosis problem if we succeed in diagnosing osteoporosis, e.g. with quantitative methods, before it becomes evident in the conventional x-ray, and then start an appropriate "prophylactic" therapy, e.g. with estrogens, SERMs, estrogen-like substances, biphosphonates, calcium/vitamin D. The main problem in future will be to identify risk patients, i.e. patients who start to develop osteoporosis after the menopause. Today, we include women with premature menopause, smokers (they frequently have a premature menopause), women with a diet that is deficient in calcium/vitamin D3, lack of physical exercise, and patients with osteoporosis in the family among the risk patients.

In the EPOS study (European Prospective Osteoporosis Study) with over 7000 men and women, it was found that subjects who had a lower bone density (< –2.5 SD) at the beginning of the study presented with osteoporotic fractures of the vertebral bone 1.4 times as often as men and women with normal bone density after 3.6 years. This study complies with the requirements of evidence-based medicine in all criteria. This means that patients with a fracture risk can certainly be identified and then provided with an effective treatment.

In 1998, the European Parliament resolved that osteodensitometry must be made available in order to identify women with an osteoporosis risk, and that it should be covered by the national health services.

DEFINITION OF OSTEOPOROSIS

The human skeleton consists in roughly equal parts of basic substance and hydroxylapatite. In osteopenia and osteoporosis, this ratio is more or less preserved, but the total bone mass is reduced.

The Consensus Conferences in Copenhagen 1990, Hong Kong 1993 and

Amsterdam 1996 defined osteoporosis as follows: "Osteoporosis is a systemic bone disease characterized by low bone mass and pathological structure changes in the bone tissue, that leads to increased frailty of bone and fracture risk. The baseline bone mass, extent and duration of bone mass loss probably determine whether osteoporosis will occur." This definition contains three key concepts of osteoporosis:

- bone mass (how much is still left),
- loss of bone mass (how much is lost), and
- structural changes (how the bone is structured).

In contrast to earlier years, the focus is now more on the pathological changes in structure, e.g. how the trabeculae are linked, especially since they can now be made visible and measured not only *in vitro*, but also *in vivo* (Fig. 1).

In addition, the WHO quantifies osteoporosis, based on the bone mass, as follows:

- > –1 SD (T-score) normal
- < –1 to > –2.5 (T-score) osteopenia
- < –2.5 SD (T-score) osteoporosis

(1 SD ~ 10%) DXA equipment)

The T-score is the bone density with reference to women between 20 and 45 years of age (peak bone mass); without fractures = preclinical osteoporosis, with fractures = manifest osteoporosis (< –2.5 SD).

With quantitative computertomography scans, it is now possible to identify the cancellous and cortical bone density of the radius and tibia with a reproducibility of ± 0.3% in a mixed collective. This distinction between cancellous and cortical bone substance is extremely important because these are two different systems that react differently to pharmacological therapy.

Corticosteroid osteoporosis and osteoporosis associated with anorexia nervosa are almost exclusively characterized by loss of cancellous bone rather than loss of cortical bone.

Histological-morphometrical and quantitative computertomography stud-

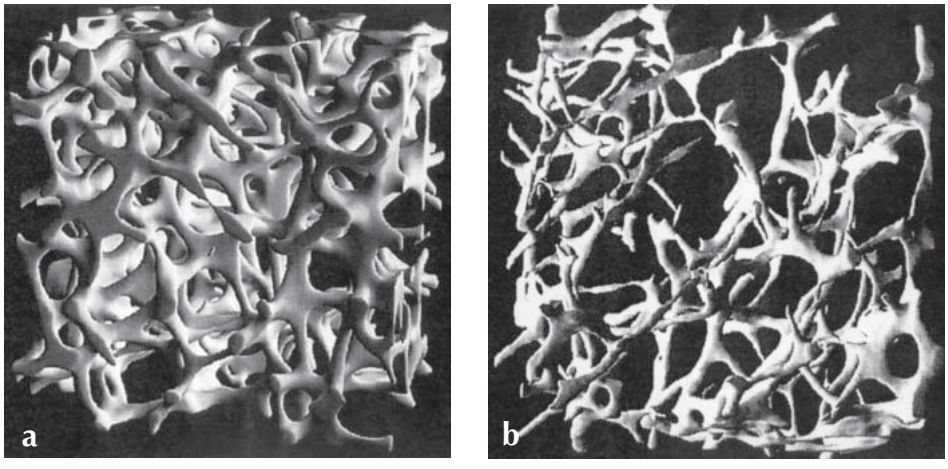

Figure 1. Normal (1a) and osteoporotic (1b) bone structures (cancellous bone, vertebra) (µCT 20, Scanco Medical Ltd., Zurich).

ies indicate that osteoporosis develops in episodes. In the postmenopause, a higher bone turnover (increased formation and destruction) is identical with rapid loss of bone ("fast-bone-loser"). Although there is rapid bone loss with an annual rate of about 7 to 10% after the onset of menopause (in terms of the total group), not all women are affected. Only about 34% of women are affected, and at risk to develop osteoporosis.

Vice versa, it has proved erroneous that there is stability in severe age-related osteoporosis (formerly referred to as senile osteoporosis), i.e. that bone formation and bone destruction are balanced. In these forms of osteoporosis, a fast-loser state is found in about 75% of the patients (Fig. 2).

Based on these considerations, it is clear that treatment of osteoporosis with formation-stimulating and destruction-inhibiting substances must be differentiated. In stability (e.g. in slow-loser patients), drugs that promote formation and in fast bone loss drugs that inhibit destruction can be used (Table 1).

In other words, osteoporosis is not a uniform disease.

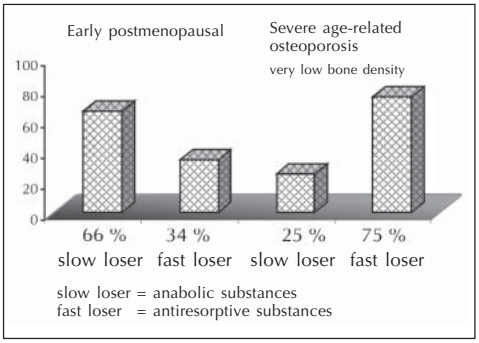

Figure 2. Fast bone loss in 34% of peri-/early postmenopausal patients and in 75% of patients with severe (age-related) osteoporosis.

Secondary Osteoporosis

In contrast to primary osteoporosis, the causes for secondary osteoporosis are known (e.g. hypogonadism in women, anorexia nervosa, e.g. in professional dancers and athletes).

Hypogonadism in women

Apart from postmenopausal osteoporosis, accelerated bone loss may also occur in women after ovarectomy, and in cases of estrogen deficiency due to hyperprolactinemia. These functional disorders of the ovaries that cause hyperprolactinemic amenorrhea are commonly found e.g. in dancers and top athletes. If such an amenorrhea lasts more than 6 months, estrogen replacement therapy is necessary, even if the trainers are not too happy about this. It is surprising to what extent this problem is negated or played down. This form of secondary osteoporosis, which is also referred to as "marathon runner osteoporosis", is closely associated with anorexia nervosa and has similar psychological behavior patterns, including e.g. the physical hyperactiv-

Table 1. Drugs that stimulate bone formation and inhibit bone destruction.

Substances that stimulate bone formation
- Fluorides
- Anabolics
- Estrogens at high doses (implants?)
- D-hormone preparations
- PTH injections

Substances that inhibit bone destruction
- Estrogens
- Calcitonin
- Bisphosphonates
- Anabolics (anti-catabolics)
- D-hormone preparations
- Calcium/Vit. D

ity that is best described as "being driven" in some patients.

It is also important to remember that an estrogen deficiency may be present after hysterectomy, even if the ovaries are left surgically intact, depending on the surgical technique (intra-operative disturbance of blood flow to the ovaries?). Therefore, it should be standard practice to determine the estrogen and gonadotropin levels if there are clinical signs of hypogonadism, even if the patient denies that the ovaries were removed in the course of hysterectomy.

Turner's syndrome is a congenital form of hypogonadism in women (gonadal dysgenesis). These patients have normal female genitals, but rudimentary gonads without any function. In contrast to eunuchoidism, the patients are usually of short stature and present with dysmorphia, sphinx-like face and webbing of the neck. Radiologically, a coarse bone dystrophy with kyphosis and hypostosis can be found. If the syndrome is diagnosed late, e.g. in adulthood, we frequently find that estrogen replacement, which would be the most obvious, is unwanted in order to avoid being pushed into unwanted psychological and physical situations by the estrogen therapy.

Osteoporosis and Anorexia nervosa

Women with sustained anorexia nervosa also frequently present with a marked, predominantly cancellous osteoporosis, and the treatment of these seriously underweight anorexia patients with special nutrition often results in a further marked loss of cancellous bone. The cortical bone is not involved. Especially during the phase of fast bone loss (e.g. due to tube feeding), this can be stopped with bisphosphonates (20 mg/kg body weight EHDP). The use of estrogens in patients with anorexia nervosa is usually senseless, since the rejection of estrogens including the consequences (weight gain!) is characteristic of the disorder. Instead of estrogens, D-hormone metabolites and even bisphosphonates can be used.

Caution: Esophageal/gastrointestinal symptoms are side effects of bisphosphonates in daily practice. This could lead to a further reduction in food intake.

Diagnostic Possibilities

X-ray and densitometry

Decreased bone density results in enhanced radiation permeability, but this cannot be detected radiologically until the loss of substance reaches a level of about 30–50%. Thereby, the patient's constitution (obesity!) and the radiology technique also play a role. The same section of skeleton can only be displayed as sclerotically dense or porotically transparent by changing the technique. In addition, the assessment of a reduced radiological shadow density by one and the same investigator may vary considerably. That is the reason why the criterion "reduced radiological shadow density" is no longer regarded as sufficient for the diagnosis of osteoporosis. When assessing the degree of osteoporosis, the routine x-ray technique is not satisfactory, since modern densitometry methods are considerably more sensitive. However, with the help of x-ray techniques it is possible to determine whether vertebral deformations are present or not.

The minimum requirements for a first radiological examination are: thoracic/lumbar spine ap and lateral; lateral in

order not to overlook possible metastases, particularly in the roots of the vertebral arches. The degree of deformation can be measured semi-quantitatively and quantitatively, if necessary.

Table 2 compares 2 (of many) techniques, namely DXA and pQCT in multi-layer technique. It shows the great differences between the individual methods, both in terms of reproducibility and exposure, and in terms of the location of measurement. The most sensitive method is peripheral quantitative computertomography in thin- and multi-layer technique. It allows the density of cancellous and cortical bone to be measured either together or individually at peripheral sites (radius and tibia) with minimum radiation exposure and with a low and thus optimal reproducibility. This is important (see above), since cancellous and cortical bone represent two different systems that may change in different ways and at different rates both with regard to the development of osteoporosis and with regard to the therapy. In steroid osteoporosis and osteoporosis associated with anorexia nervosa, for example, it is mainly the cancellous and less the cortical bone that is affected, whilst in primary hyperparathyroidism it is mainly the cortical bone. In hyperprolactinemic amenorrhea in young top athletes ("marathon runner osteoporosis"), there may be an almost total loss of cancellous bone. As the rate of cancellous bone loss since the menopause is about 1 % per year in healthy women, 1–3 % in "slow-loser" patients, and more than 3 % in patients belonging to the "fast-loser" group, quantitative densitometry methods must have a very good reproducibility (the lower this value the better the reproducibility) in order to be able to measure these differences and provide useful information for the therapy decision. The cancellous bone measured at the distal radius correlates with the cancellous bone of the lumbar spine.

Indications for densitometry: see Table 3.

Important terms in osteodensitometry that play a role in this section:

T-score (Fig. 3): expresses the deviation of a measurement from the mean value of healthy women aged 20–45 (peak bone mass) in the form of standard deviation (SD).

Z-score: expresses the deviation of a measurement from the mean average bone density of a peer population in the form of standard deviation (SD). This Z-score is hardly used any more today.

Table 2. Densitometry: Comparison between the DXA and pQCT methods using thin- and multi-layer technique

Method	DXA	hrpQCT multi-/thin-layer
Measurement sites	Lumbar spine, proximal femur, radius	Radius, tibia, hand
Parameters	Integral cortical with cancellous bone	Selective cancellous and cortical bone, structure parameters (lat. film 0.2–0.3 mm)
Dimension	g/cm^2 (surface value)	mg/cm^3 (volume value)
Reproducibility	± 1–2 % (young healthy subjects)	± 0.3 % (mixed collective)
Accuracy (mineral.)	3–6 %	< 1 %
Exposure (mSv)	< 0.05	< 0.1
Time/site (min.)	approx. 10	4 slices 8 min. 16 slices 15 min.

Reproducibility: Second measurements are used to identify "fast-loser" patients and to verify whether treatment is effective or not, and whether it is necessary to change to a different medication. The reproducibility is a standard for the (in)accuracy of measurements in routine examinations, and it takes the inaccuracy of the measuring device itself, investigator factors and factors associated with the subject into account. The long-term *in praxi* reproducibility of a method determines the minimum measurement interval. The reproducibility data provided by the manufacturer is (normally) verified by a highly qualified investigator in healthy subjects, at short intervals and under laboratory conditions, which is why it often deviates considerably from the long-term reproducibility in practice. For a 95% certainty that 2 values will actually be different, they must differ not only by the reproducibility (RP), but also for statistical reasons by 2.8 x RP (%), i.e. in the event of an RP of ± 2% they must differ by at least 5.6%.

Example: If a patient with high-grade osteoporosis, who has already lost 50% of her bone mass, is examined using an osteodensitometry method with a long-term reproducibility in healthy subjects of ± 2% (e.g. DXA), then we must ask ourselves which time interval should be chosen, if e.g. a minimum change of ± 3% per year is to be detected with 95% certainty (Table 4). The measurement interval is 45 months, i.e. we must wait 45 months (= 3.7 years) before we can decide whether a change of ± 3% can be detected at all – this is unacceptable. If a method has a reproducibility of ± 0.3% (Table 4), then we only have to wait 7 months under the same conditions as above, and this period is optimal for the therapy decision.

Table 3. Indications for densitometry. These indications vary from country to country, depending in particular on the health authorities and national health services.

Confirmed indications

Manifest osteoporosis with fracture
Long-term glucocorticoid treatment
Hypogonadism
Anorexia
Chronic gastrointestinal disorders (e.g. Crohn's disease, malabsorption)
Primary hyperparathyroidism (unclear surgical indication, bone involvement)
Organ transplant (especially heart, lung, liver)
Imperfect osteogenesis
Evaluation of therapy success
Identification of slow-loser and fast-loser patients

Possible indications

Osteoporotic fractures in the family
Estrogen deficiency syndrome
Menopause before the age of 45
Primary and secondary amenorrhea
Clinically signs of osteoporosis
Radiological signs of osteoporosis (conventional x-ray)

Laboratory

Laboratory level 1 (exclusion of secondary osteoporosis): Ca, P, alkaline phosphatase, creatinine, bilirubin, GOT, GPT, BSR (electrophoresis), blood count (urine status)

Laboratory level 2 (clinical suspicion of secondary osteoporosis): 25(OH)D3 (malabsorption), parathyroid hormone, TSH, T4, testosterone, 1,25(OH)2D3 (renal osteodystrophy)

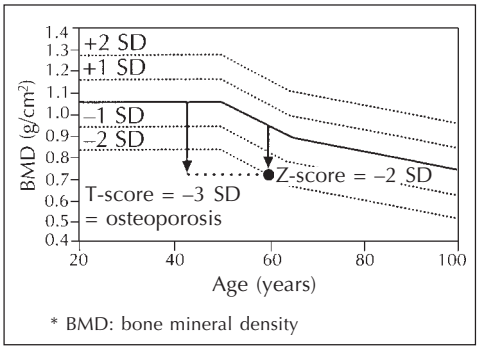

Figure 3. T-score, Z-score

Laboratory level 3 (dynamics of bone metabolism): ostasis (bone formation parameter), desoxypyridinoline/creatinine ratio (bone destruction parameter), see: Biochemical markers.

These parameters are important, if a differential therapy with bone-formation-stimulating substances in non- or slow-loser or with bone-destruction-inhibitors in fast-loser should be started.

Bone scintigraphy

If the above-mentioned radiology, densitometry and blood chemistry tests still do not allow a definite diagnosis, total-body scanning can be used. Although this method has a high sensitivity, its specificity is low. On the other hand, about twice as many metastases can be identified with scanning as with x-ray. Total-body scanning allows us to film specifically those areas that show a pathological accumulation, in order to be able to perform specific biopsies in these areas.

Bone biopsy

Since bone biopsy requires a surgical intervention and the processing of the biopsy is very complex, especially where the diagnosis of a metabolic osteoporosis is concerned, it comes quite late in the order of diagnostic procedures. In recent years, fewer bone biopsies have been conducted than in former times, since quite a few of the questions that we used to ask the pathologist or anatomist can now be answered by the physicist using quantitative methods or computerized tomography; this includes the question of activity of the osteoporosis process, the question of whether mainly cortical or cancellous bone is affected, and the question of how the cancellous structures are linked. Even biopsies can now be evaluated using computerized tomography.

A bone biopsy is indicated,

- if the scan indicates a malignant growth, and if the positive areas shown in the scan can then be biopsied;
- if a haematological disorder is suspected;

but above all

- if the previous tests did not allow a clear distinction between osteoporosis and osteomalacia;
- in all cases of "unusual" osteoporosis, e.g. in young women who are still menstruating.

Table 4. Minimum measuring intervals in months depending on bone density and reproducibility for identifying bone loss with a magnitude of ± 3 % on the 95 % confidence level. White boxes = measurement intervals < 2 years; gray boxes = measurement intervals > 2 years; * conditions as in practice

Bone density in % of peak bone mass, T-Score	Reproducibility hrpQCT* ±0.3%	±0.5%	DXA* ±1.0%	±1.5%	±2.0%	±2.5%	QUS ±3.0%	±3.5%	±4.0%	±4.5%	±5.0%
120	3	5	9	14	19	24	28	33	38	42	47
110	3	5	10	15	21	26	31	36	41	46	51
100	3	6	11	17	23	28	34	40	45	51	57
90	4	6	13	19	25	31	38	44	50	57	63
80	4	7	14	21	28	35	42	50	57	64	71
70	5	8	16	24	32	40	49	57	65	73	81
60	6	9	19	28	38	47	57	66	75	85	94
50	7	11	23	34	45	57	68	79	91	102	113
40	8	14	28	42	57	71	85	99	113	127	142

The prerequisite for a morphometric evaluation of bone biopsies is, however, that the removed biopsy is large enough and has not been destroyed, e.g. after removal from the cancellous bone of the iliac crest using a Burkhard cutter. When processing the samples, they must not be decalcified in order to avoid shrinkage and so that the tetracycline marker for identifying the mineralization front remains visible. Only preparations that have not been decalcified will allow you to distinguish whether osteoidosis or true osteomalacia is present (tetracycline marker present or diffuse). Osteoidosis is found, for example, with high bone turnover (fluoride therapy), osteomalacia with malabsorption and maldigestion. It must be pointed out time and again that the tetracycline marker is imperative for a correct interpretation of the bone biopsy. Moreover, preparations that have not been decalcified allow you to calculate morphometric structure parameters (if computerized tomography is not available), and in particular to measure the osteoblasts and osteoclasts quantitatively. These parameters can then be used later for a specific therapy, e.g. they will show whether the bone loss shown objectively by quantitative computerized tomography is due to osteoblast insufficiency or to an increase in osteoclasts. Osteoblasts can be stimulated with fluoride or with anabolic agents, whilst osteoclasts can be inhibited with estrogens, calcitonin, phosphonate, D-hormone metabolites (e.g. Rocaltrol® or Doss®), or calcium.

Biochemical bone markers (from Kränzlin, in Merlin et al.)

Bone consists of an inorganic matrix (90% collagen type I and 10% non-collagen proteins) and a mineral share (calcium hydroxylapatite). A distinction is made between metabolic products and enzymes that are formed by the bone cells, and products of the bone matrix that are released into the serum, mainly during bone destruction.

The following parameters for bone formation are available:

- bone specific alkaline serum phosphatase,
- osteocalcin,
- carboxy- and amino-terminal fractions of procollagen (propeptide type).

The bone destruction parameters are:

- hydroxyproline,
- pyridinoline cross-links,
- tartrate-resistant acid phosphatase.

Formation parameters

- *Alkaline phosphatase*

It is found not only in the bone, but also in the liver, kidneys, intestine and placenta (alkaline phosphatase, iso-enzymes). The amino acid sequence is identical, but there are differences in the tertiary structure.

Alkaline phosphatase of the bone is localized in the membranes of the osteoblasts, and it plays a role in the mineralization of the osteoid. There is no circadian rhythm, and the enzyme is relatively stable after drawing blood.

The iso-enzymes can be differentiated. Raised serum levels are found in the presence of an increased bone turnover or mineralization disorders. In osteoporosis, the values are usually within the normal range or slightly raised.

- *Osteocalcin*

Osteocalcin is identical to GLA protein. Synthesis is controlled by calcitriol. 10–20% of the non-collagen proteins

in the matrix consist of osteocalcin. The precise function is still unknown. Probably, it also plays a role in the mineralization of the osteoid. It is integrated in the bone matrix, and about 20–30% are released into the serum. It can be quantified with specific immune assays. The half-life of 4 minutes is very short, whereas the half-life of alkaline phosphatase is 1–2 days. Osteocalcin has a circadian rhythm with a maximum in the early hours of the morning. Because of rapid degradation, the samples must be processed very quickly.

Caution: Increased levels are found in renal failure and during treatment with calcitriol.

- *Procollagen/propeptide*

As mentioned above, the organic matrix consists of about 90% collagen type I. During integration in the bone matrix, amino- and carboxy-terminal fragments are separated from the procollagen type I molecule and secreted into the serum. The carboxy- and amino-terminal fragments can be measured in the serum using immune assays. Thus, they represent the osteoblast collagen synthesis. There is a circadian rhythm, but the stability after taking the sample is greater than that of osteocalcin. The clinical value has not yet been fully explored.

Destruction parameters

- *Hydroxyproline*

Nowadays, it is no longer used as a marker for bone destruction, since it requires a 3-day proline-free diet for measurement, and the collection of 24-hour urine is also problematic.

- *Pyridinoline cross-links*

Unlike pyridinoline, desoxypyridinoline is bone-specific. These substances are released during bone destruction, and eliminated as free amino acids or as telopeptides. A specific diet prior to the urine collection period is not required. The urine analysis method is very complex. It may be expected that the pyridinoline cross-links in the serum will be determined more often in future. Here, too, there is a circadian rhythm. The highest levels are found in the early morning, the lowest in the afternoon.

The advantage of this β-cross-link determination method in the serum is that a single blood sample could be used to measure osteocalcin as a formation parameter on the one hand, and β-cross-links as destruction parameters on the other hand.

- *Tartrate-resistant acid phosphatase*

This enzyme is released in the osteoclasts, the prostate and the hematopoietic system. It is very instable and must be processed immediately.

Conclusion

The osteoporosis of each patient must be examined individually, and therapeutic measures should be based on the dynamics of the disease.

For prophylaxis and for the treatment of osteoporosis, both the baseline bone mass, measured using densitometry, and the loss rate are important. Patients who lose more than 3% trabecular bone density with reference to one year, again measured by means of osteodensitometry (note reproducibility!), are referred to as "fast losers". Biochemical markers (see Lab diagnosis level 2 and "Biochemical Markers") can also be used to detect a high bone turnover (identical to fast bone loss in the postmenopause).

In practical terms, it may be assumed that progressive osteoporosis, i.e. a fast-loser condition, is present if – with reference to 1 year – there are more than 2 new vertebral fractures and/or a decrease in size by > 5 cm/year. The height should always be measured at the same time of day by the same person using the same instrument. However, the osteodensitometric methods and biochemical bone markers are, as mentioned above, more expressive.

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