Postoperative Protocol in the Prevention of Fragility Fractures in Patients with Osteoporosis-Related Fractures

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Abstract

Osteoporosis is a multifactorial disorder that requires advanced diagnostic evaluation tools. It should not be considered to be an inevitable disease entity or as a logical consequence of the physiological ageing process. Osteoporosis can be diagnosed and – more importantly – properly treated. It is therefore incomprehensible that most of the patients with diagnosed osteoporosis do not receive a specific pharmacotherapeutic treatment. Since orthopedic trauma surgeons most often see a patient with an osteoporosis-associated fracture on a first-hand basis, they, after providing adequate treatment of the fracture, must play a key role in initiating the primary diagnostics and therapy according to national or international guidelines for patients with previous osteoporotic fractures. Treatment should be closely coordinated with general practitioners so that a continuation of the therapy initiated in the hospital can be guaranteed. Basic measures for fracture prevention, including dietary supplements of calcium and vitamin D, should be recommended and implemented for all patients, whereas only those patients with the diagnosis of a manifest osteoporosis should receive a specific pharmacotherapy. Antiresorptive and anabolic drugs that are licensed for the treatment of men or postmenopausal women with osteoporosis have been shown to effectively reduce the incidence of vertebral and non-vertebral fractures. An evaluation of the treatment efficiency should also be performed, such as routine clinical re-evaluation and the measuring of the bone mineral density by dual X-ray absortiometry, every 18–24 months after the initiation of the pharmacotherapy.

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Introduction

Osteoporosis is characterized by the loss of bone mass and micro-architectural deterioration of bone tissue, leading to an increased risk of fractures (Figure 1). The incidence of osteoporosis-associated fractures exceeds even the combined incidence of breast cancer, stroke, and coronary heart disease and is not only an enormous clinical challenge but also a great economic burden to society.

Based on the World Health Organization (WHO) data, osteoporosis is among the ten most common diseases, with 8 million affected individuals in Germany and more than 45 million worldwide [1].

Osteoporosis is not a newly identified disease. There are descriptions of 4000-year-old Egyptian mummies with a dowager's hump, and the first reference to osteoporosis in scientific literature appeared approximately 200 years ago. The English surgeon John Hunter discovered the process of bone turnover, which today is known as remodeling, and Sir Astley Cooper revealed that the loss of bone mass at higher ages promotes fractures [2]. Jean Georges Chretien Frederic Martin Lobstein, a German-born French surgeon and pathologist, noticed in the 1830s that some patients' bones were riddled with larger than normal

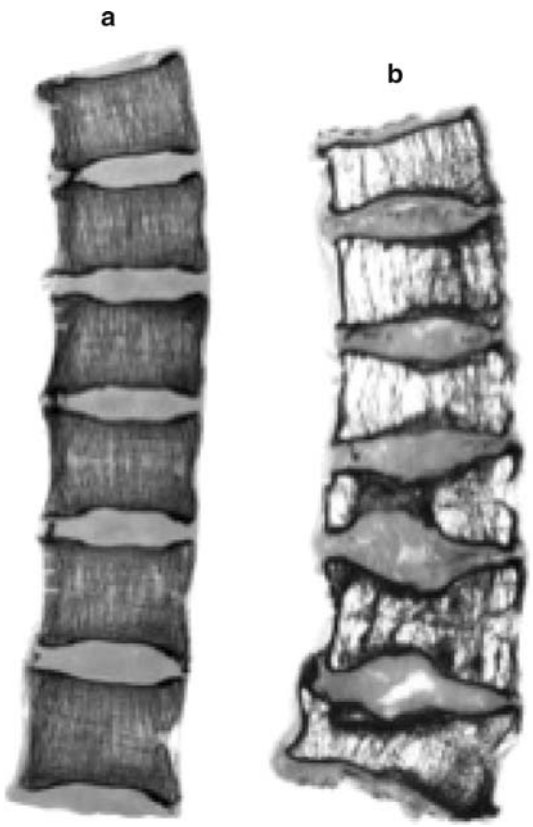

Figure 1. Contact X-ray of the thoracic spine with structural changes in the development of osteoporosis. a) Bone micro-architecture of the thoracic spine in a skeletal healthy 76-year-old female. b) Advanced osteoporosis with multiple vertebral body fractures in a 78-year-old female. Contact X-ray, 4-mm-thick sagital layer of the thoracic spine (thoracic vertebral bodies 7–12).

holes, and he coined the term osteoporosis [3]. In the 1940s, Sir Fuller Albright defined postmenopausal osteoporosis and began treating women with estrogen [4]. The conception of osteoporosis in the following years was determined by the distinction of two types of osteoporosis: Type 1 or ''postmenopausal osteoporosis'', caused by a lack of estrogen, and Type 2 or ''senile osteoporosis'', which occurs in women and men over 70 years of age in association with acalcinosis and decreased bone formation. This concept was subsequently replaced by a new understanding of osteoporosis that highlights the multiple different pathogenic mechanisms which interact and cause the loss of bone mass and the deterioration of micro-architecture.

Osteoporosis often remains asymptomatic over many years – until fractures occur, leading to functional deficits, reduced quality of life, and increased morbidity and mortality. Based on studies on hip fractures that have shown that the 6-month mortality rates are up to 20–30% higher among patients with such fractures [5], it is even more important to identify those patients at higher risk of developing osteoporosis. In addition, patients that already suffer from osteoporosis should be treated at an early stage. Since orthopedic trauma surgeons are the first medical professionals who treat patients with an osteoporotic fracture, they play a key role in initiating the appropriate diagnostic evaluation and the therapy for treating this disease, if present, after providing adequate treatment of the fracture that led to the presentation of the patient in the first place. To take over and fulfill this professional obligation is even more important since studies have demonstrated that a pharmacological therapy with bisphosphonates reduces the incidence of further fractures in patients with osteoporosis up to 60%, independent of age [6].

Recommendation for the Initiation of a Basic Evaluation for Osteoporosis

Independent of age all patients suffering from osteoporosis-associated fractures after only a mild or trivial trauma should undergo a basic evaluation for osteoporosis. In many cases, it has not been well defined just which fractures are associated with – or caused by – a decreased bone mass, i.e., which are fragility fractures and which are caused due to inappropriate, excessive mechanical loading. In general, osteoporotic fractures are associated with falls from a sitting or standing position.

Although the correlation between non-vertebral fractures and the risk factor for further fractures does not display the same power as that between vertebral fractures and the risk of further fractures, studies have shown a strong correlation does exist for many non-vertebral fractures.

Stress fractures, which often occur in younger patients, are of a different pathoanatomic and mechanic entity. Although reduced bone strength is considered to be a risk factor for the development of fractures after repeated mechanical loading, studies have been unable to demonstrate a causative relationship. Consequently, stress fractures should not be compared to osteoporosis-associated fractures.

Patients without fractures but showing radiological signs of decreased bone mineral density should not routinely undergo osteoporosis diagnostic testing. Signs of a possible osteoporosis are only visible on conventional X-rays when a significant bone loss has already occurred. Wagner and colleagues demonstrated that even in patients with T-scores below –3.0,

Table 1. Important laboratory parameters within the diagnostic evaluation of osteoporosis and other possible osteopathies. (FSH: Follicle stimulating hormone; BAP: bone alkaline phosphatase; DPD: deoxypyridinoline; AP: alkaline phosphatase; TSH: thyroid stimulating hormone; LH: luteinizing hormone; PTH: parathormone).

Diagnoses to be proved or disproved	Parameters to be measured
Osteoporosis	Calcium, phosphate, osteocalcin, DPD crosslinks, AP, BAP, vitamin D
Osteoporosis due to metabolic disorders	Estrogen, FSH, TSH, LH, cortisol, testosterone, Mastcell-Tryptase
Osteomalacia	Vitamin D, calcium, phosphate, osteocalcin, AP
Renal osteopathy	Creatinine, calcium, phosphate, vitamin D
Primary hyperparathyroidism	Calcium, phosphate, PTH
Secondary hyperparathyroidism	Calcium, phosphate, PTH
Paget disease of bone	AP, BAP, DPD crosslinks
Primary or secondary bone malignancies	Serum protein electrophoresis, DPD crosslinks

more than 20% of the findings, as seen on conventional X-ray images, were false negatives [7]. Therefore a guideline-based osteoporotic diagnostic evaluation should only be initiated when other risk factors – such as a family history of osteoporosis, personal history of fractures after mild trauma, smoking cigarettes, multiple falls or immobility – are present [8].

Specific Diagnostic Evaluation of Osteoporosis

The recommended diagnostic evaluation includes the patient's history for specific osteoporotic risk factors, clinical evaluation, dual X-ray absorptiometry (DXA), laboratory investigation, and conventional X-ray images of the thoracic and lumbar spine. The aim of the specific diagnostic evaluation is to determine a 10-year fracture risk based on the personal risk profile and, according to the S3 guidelines of the Umbrella Association of German-Language Scientific Osteological Societies (DVO), to treat those patients with a 30% predicted risk of osteoporotic fractures occurring within 10 years [8].

Since the presence of previous vertebral body fractures increases the risk for further fractures markedly, vertebral fractures should be excluded in all patients with a history of sudden severe back pain or a loss of more than 2 cm of height [9]. In addition, ''Chair rising'' and ''Timed up and go'' tests, which are valuable diagnostic tools for evaluating muscular function, should be assessed to evaluate the personal risk of falling. Finally, falls should be documented accurately [9, 10].

Particulary younger patients with non-specific fractures should be evaluated for secondary osteoporosis, which can occur in 5% and needs specific treatment. The most common forms include hypogonadism, hypercortisolism, hyperparathyroidism, systemic treatment with steroids, renal failure with creatinine serum levels of 2–3 mg/dl, malassimilation, mastocytosis, and anorexia nervosa.

Specific diagnostic evaluations for osteoporosis include the performance of a bone mineral densitometry measurement. Although there are many different measuring methods, such as quantitative ultrasound and pQCT (peripheral quantitative computerized tomography), DXA is the preferred method since, to date, all major therapeutic studies have been based on this procedure [11]. The recommended treatment of the S3 guidelines are also based on T-scores derived from DXA.

DXA values should be measured in the lumbar spine (vertebrae L1–L4) and in both proximal femurs, with the lowest of the determined values being used for further calculations. The ''T-score'' is a derived parameter representing the difference between the patient's bone density and the average value in a population of normal 20- to 40-year-old people, expressed in standard deviations from the mean [8]. However, DXA is of limited use in patients with vertebral body fractures or degenerative changes in the lumbar spine. In these cases only T-scores of the proximal femur should be used. Patients with vertebral body fractures and two hip prostheses cannot undergo DXA osteodensitometry, but they should be treated immediately with a specific pharmacotherapeutic program. Normal values in the DXA osteodensitometry accompanied by a vertebral body fracture should lead to a consideration of a differential diagnosis, and secondary causes of osteoporosis must be ruled out.

Basic osteological laboratory investigations, as an additional important diagnostic tool, should always be performed after low-energy fractures to exclude secondary osteoporosis and other important bone pathologies that can also be associated with a decreased bone mineral density (Table 1). Clinical trials,

such as the study of osteoporotic fractures or the Fracture Intervention Trial (FIT), identified hyperthyroidism combined with a decreased serum thyroid stimulating hormone (TSH) level as risk factor for postmenopausal vertebral body fractures [12, 13].

However, if the diagnostic tools mentioned above cannot diagnose secondary osteoporosis or other osteopathologies, an iliac crest bone biopsy should be performed. Evaluation of undecalcified bone specimens will allow for a reliable quantitative and qualitative analysis of mineralized bone tissue, unmineralized osteoid, and cellular structures to distinguish between mineralization defects (i.e. osteomalacia) and other metabolic bone disorders (i.e., mastocytosis) [14].

Treatment

An important step in the acute management of osteoporosis-related fractures is that patients be treated immediately – either operatively or non-operatively – according to the presenting fracture and that they become mobilized as soon as possible with full weight-bearing. This mobilization of patients with osteoporotic fractures as early as possible is essential for full rehabilitation and reintegration into daily life as this reduces the risk of postoperative complications, deformities, and disabilities. Several studies have shown that a delay in the stabilization of fractures for only 1 or 2 days leads to an increased morbidity and mortality [15]. Moreover, patients should also receive an adequate pain therapy according to the WHO guidelines [16]. The treatment of patients with vertebral body fractures and persisting pain despite pharmacological pain management may include vertebro- or kyphoplasty.

Independent of the immediate treatment of the presenting fracture, it is the responsibility of the orthopedic trauma surgeon to initiate the basic measures for fracture prevention after the basic diagnostic evaluation has been performed. The medical report has to contain the appropriate clinical information that will ensure that the patient, once released from the hospital or the geriatric rehabilitation institute and under the care of his/her general practitioner, will continue to receive the initially started specific pharmacotherapy. Unfortunately, although it is well known that the risk for further osteoporosis-related fractures is up to six-fold higher in patients once treated for an osteoporosis-associated fracture and diagnosed with osteoporosis; fewer than 10% of these patients receive a guideline-adapted therapy [17].

Basic Measures for Fracture Prevention

Independent of age and prior fractures, patients with a higher risk for osteoporosis should undergo basic measures for the prevention of further fractures. As early as during their hospital stay, such patients should receive an intense counseling on living habits that promote bone health.

Important factors in preventing fractures and falls are regular physical exercises aimed at promoting muscular strength and power as well as neuro-muscular coordination [18]. Moreover, other risk factors, such as underweight and smoking habits, should be abolished; simultaneously, a medication that influences bone metabolism negatively and increases the likelihood of a fall should be revised.

Basic measures for maintaining musculoskeletal health include the concomitant supplementation of calcium and vitamin D. It has been shown that a decreased calcium intake, an age- or disease-related calcium malabsorption, or a vitamin D deficiency can lead to secondary hyperparathyroidism. The active 1,25-dihydroxy vitamin D enhances the intestinal absorption of calcium and phosphate and inhibits the synthesis of parathormone (PTH). Moreover, vitamin D deficiency and secondary hyperthyroidism may not only lead to increased loss of bone mass and bone stability, but they may also affect the neuromuscular function negatively, with an increased risk of falls. Clinical trials on patients with vitamin D deficiency have demonstrated that the correction of vitamin D serum levels (with a target > 30 ng/ml) reduces the occurrence of fractures and the risk for falls significantly [19].

A study from Priemel and coworkers investigating the bone status among the Germany population has shown that vitamin D deficiency is more common than initially assumed. More than 90% of the individuals presented with vitamin D serum levels lower than 30 ng/ml. Moreover, histomorphometric analysis revealed that 20% of these showed a mineralization defect with an increased osteoid volume [20].

Specific Pharmacotherapy

Specific pharmacotherapy is indicated according to the S3 guidelines of the DVO when the 10-year risk of fractures exceeds 30%. However, the recommendation for treatment is not only based on the measured T-score but also considers age-related and present risk factors. The exceptions are vertebral body fractures, which need to be treated with a T-score lower than –2.0 independent of age. Moreover, patients with two or

more vertebral body fractures can be treated independently of the DXA osteodensitometry.

If risk factors or non-vertebral body fractures are present, then the threshold T-score for treatment can be lowered by up to one standard deviation or by considering the patient to be one decade older. The initiation of prophylactic pharmacotherapy with the aim of preventing a possible bone loss or increased risk of falls in the future is not recommended (Table 2) [8].

Pharmaceuticals considered for the treatment of postmenopausal osteoporosis can be categorized into anti-resorptive (alendronate, ibandronate, risedronate, zoledronate, raloxifene, and estrogens) and anabolic (strontium ranelate, parathormone fragment 1–34 and 1–84) drugs. All of the drugs mentioned have been proven to effectively prevent vertebral fractures and – with exception of raloxifene – peripheral fractures as well (evidence-based level A) [8]. For the treatment of osteoporosis in men, alendronate, risedronate, zolendronate, and parathormone fragment 1–34 have been approved.

When osteoporosis occurs due to low levels of testosterone, testosterone replacement therapy may be a treatment option [21].

Since there are no data available to date on age, fracture type, bone remodeling, among others, as related to choice of drug, the drug should be recommended on the basis of compliance, side effects, and practicability – with the agreement of the patient. For each drug, there is one recommended dosage for the daily, weekly, monthly, quarterly, and yearly application. With the exception of strontium ranelate, studies have been unable to demonstrate that higher dosages lead to an increased reduction of further fractures.

Bisphosphonates can either be administered orally or intravenously. The DIVA-Study for ibandronate – with four treatments per year – and the HORIZON-Fracture study for zoledronate – given once yearly – demonstrated a significant decrease in vertebral body fractures in comparison to a placebo-treated control group in the treatment of postmenopausal osteoporosis [22, 23].

Raloxifene is a selective estrogen receptor modulator (SERM) that mimics the actions of estrogen on the bone. It also works as an anti-estrogen on breast tissue and the uterus. The MORE-study has shown that raloxifene lowers the incidence of non-vertebral body fractures as well as the risk of breast cancer. In patients with a history of venous thrombo-embolism or other emboli, however, raloxifen is contraindicated [24].

Although a constant increase in PTH concentration, as found in hyperparathyroidism, causes an activation of osteclasts, resulting in bone resorption, intermittent elevations of the PTH concentration, as it occurs in the daily injections of PTH, leads to a stimulation of osteoblastic cells when the 1–34 N-terminal fragment is used. Both of the recombinant parathormones, PTH 1–34 as well as the full-length PTH 1–84, which also contains the C-terminal region of PTH, have been proven to significantly reduce vertebral and

Table 2. Dark grey boxes indicate the introduction of a specific medical treatment. This table is only applicable after full basic diagnostics. (RF: Risk factors, including peripheral fractures, history of proximal femur fractures in parents, multiple falls, smoking cigarettes, immobility, and underweight BMI <20)

Age (years)		T-Score						
Female	Male	< -4	-3.5 to -4	-3 to -3.5	-2.5 to -3	-2 to -2.5	-1.5 to -2	-1 to -1.5
50 – 60	60 – 70		+ RF	+ RF				
60 – 65	70 -75			+ RF	+ RF			
65 – 70	75 – 80				+ RF	+ RF		
70 – 75	80 - 85					+ RF	+ RF	
>75	>85						+ RF	+ RF
Vertebral fractures		Specific medical treatment indipendent of T-Score						

non-vertebral fractures. In contrast to other antiosteoporotic drugs, teriparatide (Forsteo®) and PTH 1–84 (Preotact®) are administered subcutaneously [25, 26].

Strontium ranelate increases bone formation and decreases bone resorption and is therefore used as a dual action bone agent. It has been suggested that strontium ranelate stimulates calcium-sensitive receptors and leads to a differentiation of pre-osteoblasts to osteoblasts. Moreover, the osteoprotegerin released by osteoblasts inhibits osteoclasts through binding to the Rank ligand, resulting in a decreased bone resorption [27]. Independent of the specific strontium effects, the distribution of strontium in bone already leads to an amplification of bone mineral density (BMD) measurement by DXA. The present data indicate that this factor accounts for approximately 50% of the measured change in BMD over 3 years [28]. Strontium ranelate is administered as 2-g granules in an oral suspension.

Most osteoporosis medication should be given for 3–5 years. With PTH 1–34 and PTH 1–84, the medication is limited to 18 and 24 months, respectively. A clinical follow-up evaluation should be performed 6 months after the initiation of the therapy. Repetition of the DXA is recommended in intervals after 18–24 months [8].

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