Update: Treatment of Osteoporosis
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Update: Treatment of Osteoporosis to Prevent Fractures in Traumatology

H. Schwarz, R. Thierolf

Abstract: Fractures are a highly predictive indicator of the fragility of bone secondary to osteoporosis. Therefore, the traumatologist bears the primary responsibility for the diagnosis of osteoporosis and the initiation of therapy. He is no longer responsible for mere fracture management alone as he used to be in the past. It is not sufficient to judge the adequacy of the fracture alone; rather, the entire risk constellation with regard to osteoporosis must be taken into account. Rapid action is required because the risk of subsequent fractures is highest once the first fracture has occurred. Therefore, when osteoporosis is suspected to be partly responsible for the fracture, the traumatologist must initiate further diagnostic evaluation early or perform the necessary diagnostic or therapeutic steps himself/herself. Fracture prevention includes a wide range of options. The therapy must be planned such that the risk of fracture is reduced rapidly and effectively. The best basis for the diagnosis and management of osteoporosis are the S-3 Guidelines of the DVO [1], which were formulated by consensus between experts in German-speaking countries. J Miner Stoffwechs 2011; 18 (Supplement 1): 18–22.

Introduction

In current medical treatment, the patient with osteoporosis is usually confronted with two different philosophies for the resolution of his/her problems, which virtually constitute two different worlds in terms of their points of view and frequently do not cooperate with each other in a manner that would benefit the patient:

On the one hand we have the “osteoporosis specialist” who is usually an internist, rheumatologist or orthopedist. Based on thorough and well structured guideline-based evidence, and through the approach of a systematic risk screening, he identifies those individuals who are exposed to a particularly high risk of fragility fractures due to osteoporosis. When a specific threshold for an absolute fracture risk is exceeded, he institutes additional measures. However, a very small number of at-risk individuals have been identified with osteoporosis by the use of these broad-based screening investigations.

The second world is that of the traumatologist. He usually diagnoses and treats a fracture in the course of trauma. The fracture is made to heal either by conservative treatment or surgical stabilization or, in cases of osteoporotic vertebral body fractures, he achieves rapid and efficient reduction of pain by the use of minimally invasive osteoplastic procedures. After the treatment the “problem” is usually believed to have been resolved, handled, and is laid aside. The fact that elderly persons who experience fractures suffer from osteoporosis and are subject to a particularly high risk of subsequent fractures in the near future is usually not taken into account. Further conclusions are not drawn and the traumatologist believes his task has been concluded.

However, exactly at this point in time there are very good – and from the traumatologist’s perspective very feasible – chances of protecting the patient from subsequent fractures.

Fractures as a risk indicator for osteoporosis

Fractures are the sole and actual pathogenic aspect of osteoporosis. Osteoporosis is defined as a structural and quantitative weakening of bone that results in increased fragility. The greater the weakening of bone, the less severe does the traumatic incident need to be, and the greater is the likelihood of bones becoming fractured.

While the remaining risk factors (Table 1) are merely surrogate parameters that serve to draw conclusions about the risk of fracture on the basis of statistical correlation, the osteoporotic fracture is, so to speak the direct “experiment” that corroborates the fragility of bone, in some cases in the context of a high susceptibility to falls or more hazardous falls. When such a fracture occurs, a hypothetical risk becomes an obvious diseased condition.

Accordingly, the fact of an osteoporotic fracture is indicative of the highest quantitative risk of fracture. While a change in bone density (DXA) by one standard deviation is expressive of a two-fold higher risk of fracture [2], the fact of pre-existing vertebral body fractures indicates a five-fold higher risk [3].

At the ASBMR Congress in Cincinnati in 1997, Sanders et al [4] presented statistics which showed that 66.7 % of patients aged 60 to 69 years who had been hospitalized with a fracture had bone densities below a T-value of -2.5. Among those aged 70 to 79 years, the proportion was 87.2 % (Figure 1). Thus it may be concluded that the large majority of elderly persons with fractures who are referred to the traumatologist not only have fractures that require treatment but also osteoporosis...
which increases their risk of experiencing subsequent fractures, requires treatment, and is amenable to treatment.

Besides, the experienced traumatologist can draw conclusions about the enhanced fragility of bone on the basis of the location, type, and morphology of the fracture. During surgical treatment he gains immediate knowledge of the “material quality” of the bone he has worked on. Every traumatological surgeon is aware of these phenomena, but the phenomena have been very poorly documented by evidence from clinical studies.

Vertebral body fracture: the best predictor of subsequent fractures

Of the various fracture locations, the quality of risk prediction for subsequent fractures has been best investigated in respect of vertebral body fractures. From the traumatologist’s point of view, a distinction between “non-clinical” (so-called morphometric fractures) and “clinical vertebral fractures” is an unusual and strange approach.

A morphometric fracture is defined as a reduction in the height of the vertebral body by > 20% compared to the adjacent vertebral body, the previous medical report, or the unchanged anterior or posterior margin of the same vertebra, provided there is no evidence of the reduction in height being caused by any factor other than a fracture.

This distinction is based on the experience that about 30% to 40% of vertebral fractures are not experienced as fractures by the patient or not identified as such by the doctor, although they are a very strong predictor of subsequent fractures [5]. In the EVOS study it was shown that fractures with collapse of the dorsal plate on the X-ray are frequently not recognized as osteoporotic vertebral body fractures. Forty-eight per cent of the existing vertebral body fractures in women and 80% of those among men were not identified as such on X-rays [6].

In other words, it is not only relevant to identify an existing clinical fracture, but also necessary to recognize pre-existing older morphometric fractures when evaluating an X-ray, in order to determine the level of fracture risk and decide about drug treatment for osteoporosis.
While the risk of subsequent fractures is increased even in cases of clinically non-apparent fractures, the risk is much higher in cases of clinically significant fractures.

According to Genant’s classification [7], a distinction is made between three grades of severity of osteoporotic vertebral body fractures: Grade 1 with a height-reduction by 20–25 %, Grade 2 with a height-reduction of 25–40 %, Grade 3 with compression > 40 %. The risk of subsequent fracture increases in direct proportion to the grading according to Genant’s classification; this constitutes an important basis for the DVO guidelines 2009.

Furthermore, the results of the EPOS study [8] show that the risk of fracture increases not only in direct proportion to the number of existing vertebral deformities, but also that the morphology of a fracture permits a predictive statement about subsequent fractures.

It should be noted that the risk of subsequent fractures is an immediate and threatening risk for the patient. A study performed by Johnell [9] shows that the risk of subsequent fractures in the first three to six months after a vertebral body fracture is nearly two-fold higher than the risk after one year. The risk of subsequent fractures drops in asymptotic fashion to a more or less constant level, which is still several times higher than the corresponding risk in persons who have experienced no fractures (Figure 2). This proves that, with regard to the prevention of subsequent fractures, the clinician is called upon to act urgently and rapidly [10]. Therefore the German-language S3 guidelines of the DVO [1] explicitly mention the need for rapid therapeutic measures.

These facts show that, with regard to the diagnosis of fractures, the traumatologist possesses the most crucial key to the diagnosis of osteoporosis and evaluation of the level of risk of subsequent fractures. The traumatologist is obliged, more than anyone else, to initiate treatment that will prevent further fractures.

**Risk stratification**

In the majority of the guidelines used throughout the world, the indication for osteoporosis therapy to prevent fractures is currently based on risk stratification. Based on a now comprehensive body of best evidence, a person’s absolute risk of experiencing an osteoporotic fracture is calculated. Various risk factors are combined, because a statement based on a complexity of risk factors is much more accurate in terms of sensitivity and specificity compared to a statement based on a single factor.

The procedure of risk stratification is described in the following, taking into account the consensus-based S3 guidelines of the DVO for German-speaking countries [1].

An algorithm was created on the basis of valid study data. The algorithm first considers the independent risk factors of age and gender. At 10-year intervals from the age of 50 onward for women and from 60 onward for men, additional risk factors are taken into account (Table 1). “Advanced diagnostic procedures” are indicated when a patient’s individual absolute fracture risk exceeds the threshold of 20% for a cumulative risk of spinal or hip fractures in the next 10 years.

According to the DVO guidelines, these advanced diagnostic procedures consist of a detailed documentation of the patient’s medical history, clinical reports of bone density based on densitometry, a relevant laboratory investigation for differential diagnosis and to exclude other bone diseases and – if indicated – an X-ray investigation of the spine to identify potential, currently unknown vertebral body fractures.

These guidelines emphasize that, among all risk indicators of pre-existing fragility fractures, especially those of the vertebral column should be given special attention. In cases of extraspinal fractures, identification criteria such as the concomitant causal role of bone fragility or the intensity of trauma cannot be well standardized. Therefore, the guidelines underline the importance of the physician’s subjective estimation of the patient’s condition.

The indication for specific drug therapy is established when the complete diagnostic work-up for osteoporosis reveals a fracture risk in excess of 30% per the above mentioned definition and the algorithm of the DVO guidelines (Table 2).

**Identification of increased bone fragility: Consequences for the traumatologist**

For the traumatologist, the facts presented here and the requirements of the DVO guidelines which are based on general consensus signify that he plays a very important role and bears high responsibility for the diagnosis of a fracture:

1. When confronted with any vertebral body fracture with a height reduction > 25 % and in cases of multiple vertebral body fractures, he must recommend diagnostic procedures for osteoporosis.
2. In case any vertebral body fracture is identified, he must look for potential pre-existing and clinically non-apparent additional fractures.

3. In any fracture in a woman > 50 years of age or a man > 60 years of age, or in the presence of specific risk factors (Table 1), the traumatologist must raise the question of a potential fragility fracture.

4. In the individual case the traumatologist must establish the diagnosis of a high fracture risk, i.e. osteoporosis, on the basis of guideline criteria. The traumatologist is obliged to draw the attention of the physicians in charge of the patient’s subsequent care as well as the patient’s attention to the need for further steps regarding diagnosis and therapy. This is as important as ensuring appropriate further treatment of the fracture. Best evidence has been obtained for the fact that patients with fractures of the femoral neck whose osteoporotic fragility fracture is suspected and is a worthwhile measure solely from a preventive point of view.

5. Alternatively, the traumatologist may himself initiate further diagnostic steps or the required therapy.

Occasionally the question arises as to whether a bone density measurement is required for further treatment in patients with a very high risk of fractures. With reference to the DVO guidelines, consistent application of the guidelines’ algorithm verified the validity of the following criteria:

1. The diagnosis of osteoporosis can be reliably established and differentiated from other diseases associated with fragility (such as osteomalacia).
2. Patients who, according to evidence from studies, would benefit most from treatment can be identified best.
3. Therapy can be monitored best when one adheres to the guidelines’ standards.

However, it should be mentioned that there could be constellations in which the evident need for treatment would obviate the necessity to perform a bone densitometry. These include patients with a fracture constellation that demonstrates a particularly high risk, possibly also in conjunction with other parameters (such as very advanced age), and cannot undergo a densitometry. The individual physician’s judgment is the decisive factor in these cases.

The multimodality treatment approach

The treatment of osteoporosis is divided into two major categories: basic therapy and drug therapy. As mentioned in the guidelines, the treatment must encompass both categories and should not merely consist of a single medication.

Basic measures comprise the following:

1. Strengthening of muscles and bone. Bone identifies a regulated system, namely the load it is required to bear, and reacts to this requirement by means of degradation or augmentation. Furthermore, good coordination and strength protect the body from situations that cause falls as well as attenuate the severity of a fall.
2. The intake of calcium through one’s diet or other food supplements at a dose of 1000 to maximum 1500 mg daily.
3. Supplementation of 800 to 2000 IU of native vitamin D (cholecalciferol), especially in elderly persons.
4. Avoiding or minimizing other lifestyle- or drug-associated risk factors (refer to DVO guidelines).

Basic treatment is meaningful in any patient in whom an osteoporotic fragility fracture is suspected and is a worthwhile measure solely from a preventive point of view.

Options of drug therapy

Once the guideline threshold for a specific drug therapy is reached by the patient, a good portfolio of medications are available to the physician. The uppermost goal and the foremost requirement of an effective medication for the treatment of osteoporosis is that it should provide effective protection from (further) vertebral and non-vertebral fractures. The therapeutic benefit of anti-absorptive and osteo-anabolic substances is measured by the extent to which they reduce the risk of fractures. To this day we lack representative clinical studies that permit an evidence-based, comparative systematic evaluation of the individual active substances. Nevertheless, the results of clinical studies indicate that the available drug options differ in terms of their fracture-reducing properties.

The DVO guidelines include the following substances in their list of therapy options and indications of first choice for the treatment of osteoporosis: alendronate, ibandronate, risendronate, zoledronate, raloxifene, strontium ranelate, teriparatide and PTH 1-84 (estrogens/tibolone prescribed for other indications also reduce the risk of fractures).

In the meantime, more than 20 years of experience have been obtained with the most frequently prescribed substance class throughout the world, namely bisphosphonates. The guidelines list the following substances: alendronate, ibandronate, risendronate, zoledronate.

Bisphosphonates possess varying degrees of affinity to the hydroxylapatite of bone and may therefore survive for a very long period of time (several weeks to several years) on the surface of bone. Molecules of osteoclasts are phagocytosed during the degradation of bone. Modern N-bisphosphonates induce an enzyme blockade in the mevalonate metabolism of osteoclasts, which reduces bone-absorbing activity and may eventually cause early apoptosis.

All bisphosphonates act selectively only in bone tissue and have therefore not been demonstrated in any other organ. Despite several common features, the bisphosphonates differ in terms of their biochemical and pharmacological properties.

Table 2: Indication for a specific drug therapy (based on the DVO guidelines 2009)

<table>
<thead>
<tr>
<th>T-value</th>
<th>≤2,0</th>
<th>&gt;2,0 to ≤2,5</th>
<th>&gt;2,5 to ≤3,0</th>
<th>&gt;3,0 to ≤3,5</th>
<th>&gt;3,5 to ≤4,0</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(Only applicable to bone densitometry values. The efficacy of drug therapy at T-values > 2.0 has not been proven.)
with reference to gastrointestinal tolerability, binding affinity to the hydroxylapatite of bone, retention time and distribution in bone, and anti-absorptive potency. These aspects will be not addressed here in detail.

Earliest possible institution of treatment is of prime importance. As mentioned earlier, the risk of subsequent fractures is highest after an individual has sustained a fracture. On the other hand it has been shown that a fracture-reducing effect can be achieved very early (Table 3). This fact has been proven by best evidence for alendronate just after six months and has also been demonstrated in part for other substances from 12 months onward. This is the reason why the guidelines urge physicians to take rapid action.

The published studies consistently reveal the following: the greater the risk of subsequent fractures, the higher is the percentage of averted fractures when effective treatment is started early. Besides, it should be noted that, in a population of patients with hip fractures, the mortality of those who had undergone drug treatment was 28% below that of untreated patients [17]. Concerns about the early administration of a bisphosphonate exerting negative effects on fracture healing and that a watch-and-wait approach would be advisable, have not been confirmed thus far.

A dual effect on bone remodeling is currently postulated for strontium ranelate: this substance influences absorption as well as the formation of new bone. The ingested strontium is integrated into the newly formed bone mineral instead of calcium [18]. Thus, bone densitometry data may be influenced by the bone markedly enriched with strontium. In the two phase-III studies [19, 20], vertebral body fractures were shown to be reduced just after 12 months.

Raloxifene belongs to the group of SERMs (Selective Estrogen Receptor Modulators) that act on estrogen receptors in bone and thus primarily reduce bone degradation. The MORE study [21] showed a significant reduction of clinical vertebral body fractures after 12 months not only in women with evident osteoporosis (Table 3).

The intact human parathyroid hormone and the N-terminal amino acid fragment teriparatide stimulate the activity of osteoclasts and thus promote the construction of new bone substance. Results of phase-III studies [23, 24] show an enormous gain of bone mass mainly in the trabecular region. Simultaneously, the risk of vertebral fractures was reduced after 18 and 24 months, respectively.

The RANK-ligand antibody Denosumab will be approved shortly for the treatment of postmenopausal osteoporosis. The anti-absorptive effect of this entirely human monoclonal antibody is achieved by selective inhibition of RANKL, which is one of the most important extracellular signal transmitters for regulation of bone absorption. In the marketing authorization study [25] for the treatment of postmenopausal osteoporosis, denosumab was compared with placebo and was found to reduce the occurrence of vertebral body fractures demonstrable on radiographs after 12 months.

### Table 3: Rapidity of the reduction of fracture risk (Data from phase-III studies – no direct comparative studies)

<table>
<thead>
<tr>
<th>Vertebral fractures</th>
<th>Morphometric</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate [14]</td>
<td>12 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Ibandronate [15]</td>
<td>24 months</td>
<td>36 months</td>
</tr>
<tr>
<td>Risedronate [11–13]</td>
<td>12 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Zoledronate [16]</td>
<td>12 months</td>
<td>36 months</td>
</tr>
<tr>
<td>Strontium ranelate [19–20]</td>
<td>12 months</td>
<td>not available</td>
</tr>
<tr>
<td>Raloxifene [21–22]</td>
<td>36 months</td>
<td>12 months</td>
</tr>
<tr>
<td>PTH (1–34) [23]</td>
<td>21 months</td>
<td>not available</td>
</tr>
<tr>
<td>PTH (1–84) [24]</td>
<td>18 months</td>
<td>not available</td>
</tr>
<tr>
<td>Denosumab [25]</td>
<td>12 months</td>
<td>not available</td>
</tr>
</tbody>
</table>

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