Recommendations on the diagnosis and treatment of osteoporosis. Reducing the incidence of fractures through effective prevention and treatment

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Abstract

Aim

To develop recommendations on the diagnosis and treatment, both pharmacological and non-pharmacological, aimed to reduce the incidence of osteoporotic fractures in Poland.

The general strategy has been founded on a two-step diagnostic and therapeutic approach (see the main algorithm):

- Step 1: selective screening based on the physical examination and the presence of clinical risk factors for fractures, in order to stratify patients for undertaking preventive measures or further diagnostic evaluation of osteoporosis.

- Step 2: deciding on pharmacological treatment based on the estimation of the 10-year absolute fracture risk made as a result of a comprehensive diagnostic evaluation based on fracture risk factors, densitometry, determination of bone turnover markers and identification of asymptomatic vertebral fractures.

Pharmacological treatment in primary osteoporosis is undertaken when the 10-year fracture risk exceeds 20% and following an osteoporotic fracture. Due to the risk of subsequent fractures, each osteoporotic fracture is an indication for immediate initiation of pharmacological intervention. The efficacy of treatment and persistence on treatment are verified by biochemical and densitometric assessments. In secondary osteoporosis, the management procedures apply, except that they additionally take into account the requirements arising from treatment of the underlying disease. Systemic glucocorticosteroid treatment is included in the diagnostic and therapeutic algorithm as one of the major risk factors for osteoporosis. Fracture prevention and antifracture treatment should be complemented by appropriate recommendations on the diet, rehabilitation and prevention of falls.

Methods

A multidisciplinary group of experts conducted an analysis of publications in the Medline and Cochrane databases related to the diagnosis, prevention and treatment of osteoporosis published in English between January 2001 and June 2007. The levels of evidence and grades of recommendations were evaluated in accordance with the guidelines of the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk) (Appendix 3). The grades of recommendations A, B, C and D are given in brackets in the summary of recommendations.

Summary of recommendations

1. The diagnostic evaluation and treatment of patients with osteoporosis is aimed to prevent osteoporotic fractures and, if fractures are present, to initiate effective pharmacological treatment (parallel or subsequent to orthopaedic management).

2. Competences general practitioner include: identification of patients at risk for fractures (based on the physical examination and a history of risk factors for fractures), recommendation of preventive measures and referring patients at risk for fractures to an osteoporosis outpatient clinic or other specialists, followed by continuation and monitoring of patient compliance with the treatment protocols prescribed by those clinics or specialists.

3. A major role in the prevention of osteoporosis is played by the optimisation of intake of calcium (in line with relevant recommendations), protein (1.2 g/kg), potassium (over 3500 mg/day) and magnesium (over 300 mg/day) (B). Appropriate supply of vitamin D reduces the risk of fractures

as a result of direct effects on bone and the optimisation of the neuromuscular status also leads to a reduction of falls (A).

4. The mainstay of diagnostic evaluation is the differentiation between primary and secondary risks of fractures. In cases of secondary osteoporosis, it is essential to treat the underlying illness before osteoporosis proper is treated. The risk is especially high in the case of glucocorticosteroid therapy of more than three months' duration. Although the demonstration of pathological (non-osteoporotic) nature of the fracture or bone loss may require further specialist investigation, it does not preclude the need for symptomatic management of the bone loos at an osteoporosis center.

5. A comprehensive assessment of the skeletal risk factors for fractures includes an evaluation of the 10-year fracture risk based on densitometry, bone turnover markers, morphometry and selected fracture risk factors (B).

6. A osteoporosis consultant is responsible for verification of the initial diagnosis of osteoporosis and for the initiation of preventive and therapeutic management appropriate to the risk, based on the comprehensive evaluation of the 10-year fracture risk (B).

7. Patients with the 10-year fracture risk of less than 10% are recommended to modify their lifestyles, prevent falls and to improve the overall function of the locomotor system, especially the neuromuscular system, through appropriate rehabilitation and nutritional interventions. High (>20%) risk of fractures is an arbitrary criterion for initiation of pharmacological treatment.

8. Selection of drugs with the highest antifracture efficacy should be guided by the underlying mechanisms of osteoporosis. Anticatabolic drugs are most appropriate in patients with high bone turnover (B), while proanabolic drugs or drugs with mixed mechanisms of action demonstrate efficacy irrespective of bone turnover (B).

9. Hormone therapy (HT), oestrogens and progesterone in postmenopausal women an testosterone in men with hypogonadism, having considered the potential risks, prevents bone loss and reduces the risk of fractures (A).

10. Bisphosphonates are the most commonly used anticatabolic drugs whose antifracture efficacy is best documented both in the vertebral column (alendronate, risedronate, ibandronate) and non-vertebral sites, hip (alendronate, risedronate) (A). Due to their low bioavailability strict compliance with the administration directions is very essential. The highest antifracture efficacy has been demonstrated in patients with high bone turnover managed with alendronate (B).

11. Strontium ranelate is a drug with a dual mechanism of action (proanabolic and anticatabolic) whose antifracture efficacy is well documented in the vertebral column (A) and all the non-vertebral sites, including the hip (A). The drug is administered once daily.

12. Raloxifene (an anticatabolic SERM) shows a documented antifracture efficacy in the vertebral column only. Thanks to the additional antineoplastic effects it may be recommended for women at an increased risk for breast cancer. The risk of thromboembolism is the site of its major adverse reactions (A).

13. Calcitonin (an anticatabolic drug) demonstrates a documented antifracture efficacy in the vertebral column. Thanks to its analgesic action it is recommended in the acute post-fracture period.

14. Teriparatide (an anabolic drug). Despite the documented favourable antifracture effects in all the sites of the skeleton in patients with advanced osteoporosis, its use is limited due to its high cost, the 18-month treatment protocol and administration in the form of subcutaneous injections (A).

15. Combination treatment. There is no evidence of synergistic antifracture efficacy. Sequential therapy mainly consists in teriparatide treatment, which may precede bisphosphonate treatment (B).

16. As it is very difficult to ensure patient persistence on patients in long-term treatment, excellent patient-doctor co-operation and appropriate treatment monitoring by means of densitometric and bone metabolism assessment are becoming increasingly important. Appropriate evaluation of therapeutic progress significantly affects the antifracture efficacy of treatment (B).

Introduction

Advanced osteoporosis, as a result of the reduced mechanical resistance of the skeleton, manifests in fractures. Vertebral fractures are the earliest to develop. The most dangerous, in terms of consequences, are hip fractures. According to the commonly accepted definition, osteoporosis is a systemic skeletal disease, characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. The currently adopted densitometric criteria for the diagnosis of osteoporosis have revealed many deficiencies. Bone mass density (BMD) measured by densitometry only partially contributes to mechanical bone strength. Approximately 50% of fractures occur in women who, according to the densitometric criteria, do not have osteoporosis. It is becoming increasingly recognised that qualitative parameters, such as age and bone turnover, in addition to bone mass measured densitometrically, are essential elements that define the actual mechanical bone strength. Prevalent asymptomatic vertebral fractures as well as all low-trauma clinical fractures are an additional element that confirms the low mechanical resistance of bone and the high risk of subsequent fractures.

In order to increase the effectiveness of diagnosis and treatment, a two-step interventional approach to reduce the number of osteoporotic fractures is proposed for primary care physicians and specialists to be implemented in a stepwise fashion. Competences of a general practitioner include: identification of patients at risk for fractures based on the history and physical examination, comprehensive prevention of osteoporosis and fractures as well as the initiation or continuation of long-term management of osteoporosis recommended by made by an osteoporosis consultant. Responsibilities of a osteoporosis consultant involve verification of the diagnosis of osteoporosis and selection of appropriate management options based on a comprehensive assessment of the 10-year fracture risk (calculated fracture risk). Therapeutic management of osteoporosis consists of two integral elements: non-pharmacological management (nutritional interventions, rehabilitation and lifestyle modification) and pharmacological management. They improve the mechanical bone strength and prevent a first fracture or reduce the risk of subsequent fractures. Pharmacological management should take into account the mechanisms of action of drugs used in osteoporosis. The available antifracture treatments include anticatabolic treatments (bisphosphonates, hormonal therapy, SERMs, calcitonin), proanabolic treatments (teriparatide) or dual-action treatments (strontium ranelate). When selecting the drug, its mechanism of action should be taken into consideration. As far as drug treatment is concerned, it is the law in Poland to strictly follow the approved therapeutic indications. The increasing body of analyses assessing the cost effectiveness of the various diagnostic and therapeutic strategies allows one to optimise the costs of the diagnosis and treatment of osteoporosis.

Definitions

Definition of osteoporosis

The US National Institutes of Health (NIH) define osteoporosis as a disease of the skeleton characterised by an increased risk of fractures resulting from reduced mechanical bone strength. Mechanical bone strength depends on bone mineral density and the quality of bone tissue.

Definition of an osteoporotic fracture

Given the absence of a commonly adopted definition and the fact that low-trauma (pathological) fractures may occur for reasons other than osteoporosis (cancer, bone cysts, osteomalacia etc.) the following definition is recommended: an **osteoporotic fracture** is a fracture that is disproportionate to the causative forces which occurs following a fall from the patient's own height, after all other causes have been ruled out (such as pathological fractures).

Criteria

A. Clinically, osteoporosis is characterised by fractures whose risk increases with age. The presence of an osteoporotic fracture is clinically synonymous with severe disease.

B. The criterion for initiating pharmacological intervention in osteoporosis is met when the 10-year absolute fracture risk defined for a given age and sex following an analysis of fracture risk factors reaches 20%.

C. In patients below 50 years of age, with secondary osteoporosis where it is not possible to calculate of the 10-year fracture risk based on the currently available data, the criterion for intervention should consist in the bone loss relative to sex and age (Z-score) (see the detailed recommendations).

Tasks of general practitioner

Goals for general practitioner in the primary care setting:

1. To perform selective screening based on the presence of the clinical risk factors for fractures and the physical examination aimed to identify patients requiring prevention or further evaluation.
2. To prevent falls and eliminate the nutrition- and lifestyle-related risk factors for fractures.
3. To refer the patient to an osteoporosis center or other metabolic bone unit.
4. To implement the recommendations of the osteoporosis outpatient clinic and other specialist outpatient clinics with particular attention to patient compliance with long-term drug treatment.

Competences of a general practitioner include: identification of patients at risk for fractures, selection and implementation of measures that prevent fractures and the monitoring and continuation of an osteoporosis treatment protocol recommended by other specialists.

Recommendations for general practitioner

RECOMMENDATION 1. INITIAL MANAGEMENT

Initial management involves identification of patients at risk of fractures and includes:

- History:
- Analysis of the clinical risk factors (Table 1)
- Identification of diseases that increase the risk of secondary osteoporosis (Table 2)
- Analysis of the patient's current medication in terms of effects on bone metabolism (Table 3).

Age above 65 years for women and 70 years for men, irrespective of the other risk factors for fractures, is an indication for a comprehensive evaluation of fracture risk.

- Physical examination with an emphasis on the skeletal system evaluation.

In each case of height reduction by more than 4 cm, considerable kyphosis and a shortening of the rib-to-hip distance, lateral spine X-ray or densitometric morphometry are recommended to rule out vertebral fractures.

Table 1. Risk factors for osteoporotic fractures
Age:
Women: over 65 years of age
Men: over 70 years of age
Prevalent low-trauma fracture
BMI < 18 kg/m^2
Parental history of hip fracture
Current smoking
Past or present glucocorticosteroid treatment with at least 5 mg of prednisone for at least 3 months
Early surgical or drug-induced menopause or premature natural menopause before the age of 45

Table 2. Conditions that increase the risk of osteoporosis or cause secondary forms of osteoporosis
Endocrine disorders
Menstruation abnormalities/amenorrhoea
Hypogonadism in men
Primary hyperparathyroidism
Hyperthyroidism
Hypercortisolemia (Cushing's syndrome)
Gastrointestinal disorders
Coeliac disease and malabsorption syndromes (exocrine pancreatic insufficiency, postresection syndromes, inflammatory bowel disease etc.)
Severe liver failure
Primary liver cirrhosis
Bariatric surgery
Malnutrition states
Anorexia nervosa
Conditions resulting in locomotor system dysfunction
Inflammatory systemic rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, systemic sclerosis)
Specific and non-specific forms of osteoarthritis
Injuries of the locomotor system
Congenital anomalies of the locomotor system
Osteoarthritis affecting peripheral joints and the spine
Post-polio syndrome
Parkinson's disease
Multiple sclerosis
Alzheimer's disease
Renal failure
Neoplastic disorders

Table 3. Drugs that significantly affect bone metabolism and increase the risk of fractures
Glucocorticosteroids used at more than 5 mg/day (as prednisone) for more than 3 months
Thyroid hormones at suppression doses
Anticonvulsants (phenytoin, phenobarbital)
GnRH agonists
Aromatase inhibitors
Antimetabolites and immunosuppressants
Anticoagulants

RECOMMENDATION 2. COMPREHENSIVE PREVENTION OF OSTEOPOROSIS

This recommendation applies to all patients at risk of osteoporosis, all postmenopausal women and all men over the age of 65, and involves:

- Patient education on risk assessment and on appropriate lifestyle and nutrition.
- Elimination of risk factors for fractures.
- Calcium and vitamin D supplementation (after considering the dietary intake) in keeping with the current recommendations (see *Nutritional recommendations* below).
- For directly premenopausal women or women with menstruation abnormalities: referral to a specialist in gynaecological endocrinology.

RECOMMENDATION 3. FUNCTIONAL IMPROVEMENT AND PHYSICAL THERAPY

Functional improvement and physical therapy (in co-operation with a specialist in medical rehabilitation and a physiotherapist) as well as fall prevention should include all patients over the age of 65 irrespective of fracture risk and patients with prevalent osteoporotic fractures irrespective of age.

- **Prevention:** Increasing daily motor activity (at least one hour-long walk every day), exercises aimed to improve muscle strength and general fitness, learning to perform daily living activities in a safe manner according to appropriate motor patterns (elimination of flexion and rotation of the spine) and learning safe behaviours (safe fall), sports and leisure activities matching individual functional abilities.

- **Treatment:** Exercises focusing on the part of the locomotor system affected by dysfunction, physical therapy (analgesic and anti-inflammatory, stimulating nerves and muscles), appropriate orthopaedic devices.

- **Reduction of the risk of falls** especially in the case of more than 2 falls a year and unsatisfactory results of the “get up and go” test (Table 5). The measures are aimed to prevent falls by excluding the risk factors for falls and by minimising them during specialist treatment, by comprehensive rehabilitation, by adjusting home and work environments and by teaching patients the appropriate procedures (Annexes 1 and 2).

Table 4. Risk factors for falls

Risk factors related to the patient's condition

- A history of falls, fear of falling
- Muscle weakness
- Gait and/or balance disorders, chronic disorders impairing the function of the locomotor system, use of walking aids
- Arthralgia and arthritis
- Visual impairment
- Impairment of cognitive functions (dementia), depression, memory disorders
- Urinary incontinence
- Use of more than 4 drugs or use of psychotropic and antihypertensive drugs
- Age over 65
- Low body mass

External (environmental) risk factors

- Poor lighting conditions (e.g. inside the flat)
- Obstacles in the patient's way (moving objects, cables etc.)
- Slippery, uneven surfaces (pavements covered with ice or snow etc.)
- Lack of aids facilitating position changes (such as barriers facilitating position changes in the toilet or bathroom, non-skid mats in the bath tub or shower base)
- Transport and public traffic (means of transport without appropriate adjustments, lack of the skill of getting in and out of cars, lack of ramps, lifts and escalators)

Table 5. Screening test to assess gait and balance abnormalities: The "get up and go" test

- The patient sits on a 46 cm high-seat chair and is asked to:
  - Get up from the chair
  - Walk 3 m
  - Turn around 180 degrees
  - Return to the chair and sit down
- Duration of the test: 3 minutes
- Assessment of the time required to complete the test: the threshold adopted as a risk factor for falls is 10-14 seconds
- Assessment on a 5-point scale by the observer: 1 = normal, no risk of falls; 5 = considerably abnormal, high risk of falls

RECOMMENDATION 4. IMPLEMENTATION OF TREATMENT RECOMMENDATIONS OF OSTEOPOROSIS OUTPATIENT CLINICS AND OTHER SPECIALIST OUTPATIENT CLINICS

- Monitoring and continuation of the recommended specialist treatment protocol.
- Implementation of the orthopaedic surgeon's recommendations on antifracture measures.

RECOMMENDATION 5. LONG-TERM MANAGEMENT

Periodic (every 1 to 3 years) verification of indications for specialist treatment.

RECOMMENDATION 6. PRIMARY CARE PHYSICIAN'S RIGHTS TO MANAGE OSTEOPOROSIS

If the diagnosis of severe osteoporosis with osteoporotic fractures is made, the general practitioner may initiate drug treatment himself/herself.

Nutritional recommendations

Dietary calcium, vitamin D, protein, potassium and magnesium reduce the risk of fractures not only through effects on the mechanical bone strength parameters, but also through effects on the muscular and nervous systems, preventing falls.

In Poland, dietary vitamin D supply in children, adolescents and the elderly is insufficient.

Vitamin D not only affects the bone by regulating calcium and phosphate homoeostasis, but alters resistance to fractures through direct effects on osteoblasts, myocytes and neurons.

It is recommended that the assessment of vitamin D status should not only be based on the static parameter of serum 25(OH)D, but also on dynamic parameters, such as PTH levels. The current terminology used in the assessment of vitamin D status is summarised in Table 6.

Levels of 25(OH)D ranging form 30 to 80 ng/ml optimise bone mineral density and the function of lower extremities and reduce the risk of falls, periodontitis and fractures.

In vitamin D deficit and deficiency states, systemic stores of vitamin D are depleted (25(OH)D levels below 20 ng/ml). Replenishment of these deficiencies requires administration of 2000 IU daily for 12 weeks or 15,000 IU once weekly for 8 weeks. Multivitamin supplements are not recommended due to the high doses of vitamin A.

Table 6. Terms describing vitamin D status

	Serum 25(OH)D concentration	
	nmol/l	**ng/ml**
Deficit	0–25	0–10
Deficiency	>25–50	>10–20
Relative hypovitaminosis D	>51–75	>20–30
Recommended level	75–200	30–80
Toxic level	>250	>100

RECOMMENDATION 1. VITAMIN D

Preventive measures in patients over the age of 50 involve:

- In physically active patients: Administration of at least 800 IU vitamin D_3 from October to April and exposure of 15% of the body surface area to sunlight (without sunblock) for a minimum of 20 minutes daily from May to September.
- In physically inactive patients: Administration of at least 800 IU vitamin D_3 daily.

These measures are aimed to achieve the optimum serum concentration of 25(OH)D of 30-80 ng/ml, which not only reduces the risk of fractures and falls, but provides a 30-50% reduction of the risk of prostate, colorectal, breast and ovarian cancers.

RECOMMENDATION 2. CALCIUM INTAKE

Appropriate supply of calcium is necessary for proper bone mineralisation and contributes to the maintenance of optimum bone mass. The recommended dietary intake of calcium by age and metabolic status is summarised in Table 7.

The main source of dietary calcium should consist in food, especially milk and dairy products (Table 8). Calcium contained in dairy products is more readily assimilated and, in addition to the effects on bone tissue, reduces the amount of adipose tissue and favourably affects body composition. If the intake of dairy products is reduced, calcium supplementation is recommended. The content of elemental calcium in various salts is summarised in Table 9.

Table 7. Recommended supply of dietary calcium

Age (years)		Recommended calcium supply (mg/day)	
		WHO	**Polish National Food and Nutrition Institute**
Infants	0–0.5	360	–
	0.5–1	540	–
Children	1–10	800	600–1000
Adolescents	11–18	1200	1200
Adults	>30	800	1200
Pregnant and lactating women	>19	1200	1200
	<19	1600	
Perimenopausal women		1500	900
Postmenopausal women		1500	900
Elderly persons of both sexes >60 years of age		1500	1100

Table 8. Calcium content in selected food products

Product	Calcium content mg/100 g	Product	Calcium content mg/100 g
Milk	110–120	Broccoli	48
Yoghurt	130–170	Brussels sprouts	57
Kefir	103	Wild cabbage	157
Buttermilk	110	Cabbage	46–77
Rennet cheese	390–1380	Bean (dry)	163
Cottage cheese	55–96	String bean	65
Processed cheese	370	Soya (dry)	240
Ice cream	125–155	Nuts	58–186
Chicken eggs, whole	47	Almonds	239
Sardines in oil	330	Sunflower seeds	131
		Poppy seeds	1266

RECOMMENDATION 3. SUPPLY OF PROTEIN, MAGNESIUM AND POTASSIUM

A protein consumption of 72-87 g/day (1.2 g/kg/day) (with the minimum calcium supply exceeding 400 mg/day) reduces bone mass measured as BMD, reduces the risk of PFFs by 65% and reduces the duration of rehabilitation following an osteoporotic fracture by 25%.

Optimisation of protein intake (1.2 g/kg/day), potassium intake (over 3500 mg/day) and magnesium intake (over 300 mg/day) is recommended in the following patient populations:

- Patients over the age of 50 in order to optimise bone mass (after renal diseases have been ruled out).
- Patients with recent osteoporotic fractures in order to reduce the duration of rehabilitation (after renal diseases have been ruled out).

Table 9. Elemental calcium content in salts

Calcium salt	Calcium content (%)
Calcium carbonate	39.7
Calcium orthophosphate	36.3
Calcium chloride dihydrate	27.2
Calcium citrate	21.1
Calcium chloride hexahydrate	18.3
Calcium lactate gluconate	12.9
Calcium gluconate	8.9

Tasks of doctors at osteoporosis center

The main task of an osteoporosis specialist is to confirm the presence of therapeutic indications, to initiate treatment and, subsequently, to verify the effectiveness of treatment.

Goals for doctors at the osteoporosis center

1. To verify fracture risk due to primary and secondary causes.
2. To select appropriate preventive or therapeutic management options based on a comprehensive assessment of the 10-year fracture risk.
3. To plan a protocol for treatment monitoring and co-operation with the patient.

Recommendations for doctors at osteoporosis center

RECOMMENDATION 1. VERIFICATION OF FRACTURE RISK DUE TO PRIMARY AND SECONDARY CAUSES ON THE BASIS OF:

- Analysis of clinical risk factors (Table 1).
- Investigations differentiating between primary and secondary forms of osteoporosis (Tables 2, 3 and 12).

Demonstration of low-trauma fractures or a high fracture risk requires differential diagnosis to rule out other causes than osteoporosis, such as cancer (multiple myeloma), primary hyperparathyroidism or osteomalacia.

Table 10. Ten-year fracture risk (FR) depending on sex, age and BMD T-score (according to 2005 OSC Recommendations for Bone Mineral Density Reporting)

GREEN–low risk of fracture (<10%)
YELLOW–moderate risk of fracture (10-20%)
RED–high risk of fracture (>20%)

WOMEN

Age	T-score					
	> -2.0	-2.0 to -2.5	-2.5 to -3.0	-3.0 to -3.5	-3.5 to -4.0	< -4.0
50	Low	Moderate	Moderate	Moderate	Moderate	High
55	Low	Moderate	Moderate	Moderate	High	High
60	Low	Moderate	Moderate	High	High	High
65	Moderate	Moderate	High	High	High	High
70	Moderate	Moderate	High	High	High	High
75	Moderate	High	High	High	High	High
80	Moderate	High	High	High	High	High
85	Moderate	High	High	High	High	High

MEN

Age	T-score					
	> -2.0	-2.0 to -2.5	-2.5 to -3.0	-3.0 to -3.5	-3.5 to -4.0	< -4.0
50	Low	Low	Low	Low	Moderate	Moderate
55	Low	Low	Low	Moderate	Moderate	Moderate
60	Low	Low	Low	Moderate	Moderate	Moderate
65	Low	Low	Moderate	Moderate	Moderate	Moderate
70	Low	Moderate	Moderate	Moderate	Moderate	High
75	Moderate	Moderate	Moderate	High	High	High
80	Moderate	Moderate	Moderate	High	High	High
85	Moderate	Moderate	Moderate	High	High	High

FR <10% | FR 10-20% | FR >20% | FR – fracture risk

RECOMMENDATION 2. COMPREHENSIVE ASSESSMENT OF THE 10-YEAR FRACTURE RISK

- **Principles of the 10-year fracture risk assessment**

  Comprehensive assessment of the 10-year fracture risk integrates the results of diagnostic investigations (densitometry, assessment of asymptomatic vertebral fractures, bone metabolism

assessment) and the selected fracture risk factors (age, sex, low-trauma fractures after the age of 45 and treatment with glucocorticosteroids [prednisone 5 mg for more than 3 months]).

Integrating bone mass, age, sex and selected clinical and laboratory risk factors for fractures enables evaluation of absolute fracture risk in the next 10 years.

- **Steps in the 10-year fracture risk assessment**

a. Performance of densitometry by DXA in central sites (lumbar spine [LS], femoral neck [FN]) in keeping with ISCD recommendations and reading the 10-year risk values according to sex and age from Table 10.

The absence of indications and standards for peripheral skeleton investigations (by densitometry and quantitative ultrasound) makes it impossible to use these methods for the diagnosis of osteoporosis. Treatment monitoring with the use of peripheral devices constitutes malpractice.

b. Demonstration of a 10-year fracture risk of more than 20% is an indication to initiate drug treatment.

c. In patients with moderate risk (10-20%), the presence of any of the following risk factors shifts the absolute risk **from the moderate level (10-20%) to the high level (>20%) and suggests that initiation of drug therapy should be considered:**

- Low-trauma vertebral or proximal femoral fractures in patients over the age of 45.
- Demonstration of vertebral fractures on X-ray or densitometric morphometry.
- Long-term glucocorticosteroid treatment: prednisone at more than 5 mg/day for more than 3 months.
- Increased bone metabolism in postmenopausal women measured by bone turnover markers. The results should be interpreted in accordance with the criteria listed in Table 11.

Evaluation of the 10-year fracture risk is only possible in treatment-naive patients.

RECOMMENDATION 3. PREVENTIVE MEASURES IN PATIENTS WITH A 10-YEAR FRACTURE RISK OF LESS THAN 10%

Recommendations for patients with a fracture risk of less than 10% include: lifestyle modification, fall prevention and improvement of the overall function of the locomotor system, especially of the neuromuscular system, through appropriate rehabilitation and nutritional measures.

RECOMMENDATION 4. CRITERIA FOR PHARMACOLOGICAL INTERVENTION IN OSTEOPOROSIS

- Clinically, osteoporosis is characterised by fractures whose risk increases with age. The occurrence of an osteoporotic fracture forms the basis for the diagnosis of osteoporosis and is an indication for pharmacological treatment.

- The criterion for initiating pharmacological intervention in osteoporosis without fractures consists in the demonstration of a high (>20%) individual 10-year absolute fracture risk defined on the basis of a comprehensive analysis of risk factors in the 10-year perspective.

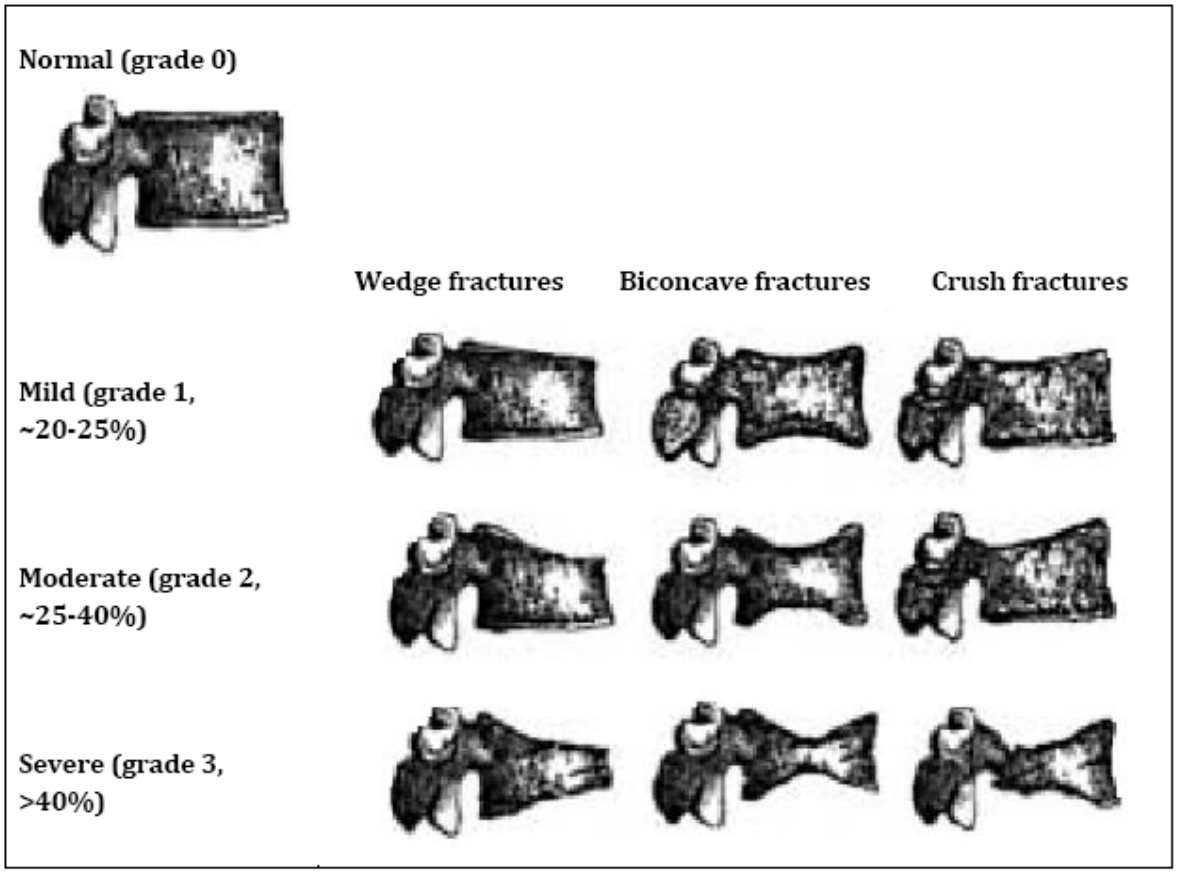
- In patients below 50 years of age, the decision is facilitated by the discovery of significant bone mass reduction in relation to sex and age (Z-score below -2 SD).

- If BMD cannot be assessed, the following may be analysed: increased bone catabolism in postmenopausal women (Table 11), presence of vertebral deformities on X-ray (Genant's criteria, Figure 1), height reduction by more than 4 cm along with the clinical risk factors for fractures (Table 1).

Table 11. Concentrations of bone turnover markers identifying postmenopausal women with increased bone turnover			
Bone turnover	**Marker of bone resorption***	**Markers of bone formation***	
	CTX (ng/ml)	**P1NP (ng/ml)**	**OC (ng/ml)**
Increased	>0.40	>30	>31
* Quantified in the serum by electrochemiluminescence (Elecsys). Fasting venous blood is collected between 7 and 10 a.m. In the case of incident fracture, blood is drawn within the first 12 hours of the fracture.			

Table 12. Biochemistry parameters in differential diagnosis	
Basic laboratory parameters	**Additional laboratory tests in differential diagnosis**
ESR	PTH (hyperparathyroidism)
Complete blood cell count	24-hour urinary calcium
Serum calcium and phosphate	Alkaline phosphatase
Serum creatinine	$25(OH)D_3$ (osteomalacia)
Total protein and serum albumin	TSH (hyperthyroidism)
If any of the above are abnormal	Cancer markers, bone marrow biopsy etc. (malignancy)

Figure 1. Semiquantitative assessment of vertebral fractures by the Genant's method



RECOMMENDATION 5. PRINCIPLES FOR THE SELECTION OF TREATMENT

- Treatment decisions in osteoporosis are based on the results of randomised, placebo-controlled clinical trials to evaluate the effects of a given intervention on fracture risk.

- The antifracture efficacy of bisphosphonates has been documented in patients with BMD T-score < -2 SD (vertebrae) and BMD T-score < -2.5 SD (hip). The assessment of bone mineral density (BMD) is therefore an essential element when deciding to start the patient on bisphosphonates.

- Only alendronate and risedronate are approved treatments for osteoporosis in men.

- The recently approved intravenous bisphosphonates (ibandronate 3 mg every 3 months, zoledronate 5 mg every year) provide effective treatment to patients with contraindications to oral products (such as directly following vertebral or hip fractures, following strokes etc.), with gastrointestinal diseases or intolerant of oral bisphosphonates. This form of treatment may also be associated with considerably improved adherence to therapy.

- The antifracture efficacy of strontium ranelate has been documented in women with osteoporosis within a wide age range, including women over the age of 80, and in women with BMD values consistent with osteopenia according to WHO. Taking into account the anabolic action component, the drug may be used irrespective of the rate of bone metabolism.

- Raloxifene should be considered in postmenopausal women at a lower risk of nonvertebral fractures, hyperlipidaemia, but most of all at an increased risk of breast cancer. Treatment with the drug is associated with an increased risk of venous thromboembolism.

- The specific analgesic action of salmon calcitonin may be useful on an on-demand basis following symptomatic (painful) vertebral fractures and in patients with chronic pain syndromes in the course of osteoporosis.

Selection of drugs with the highest antifracture efficacy should be guided by the underlying mechanisms of osteoporosis. Anticatabolic drugs are most appropriate in patients with high bone turnover, while proanabolic drugs or drugs with mixed mechanisms of action demonstrate efficacy irrespective of bone turnover.

RECOMMENDATION 6. PHARMACOLOGICAL TREATMENT IN POSTMENOPAUSAL WOMEN

- Calcium and vitamin D supplements are the mainstay of prevention and the necessary complement of osteoporosis treatment. The recommended daily doses of vitamin D_3 and calcium are 800-2000 IU and 500-1500 mg, respectively (see *Nutritional recommendations* above).

- Bisphosphonates (alendronate, risedronate, ibandronate, zoledronate) demonstrate antifracture efficacy in all types of osteoporotic fractures: vertebral, hip and other peripheral fractures. Their long-term efficacy in increasing BMD and their safety have been confirmed.

- Alendronate is most commonly used at the dose of 70 mg once weekly, which ensures better patient compliance than the dose of 10 mg daily. Alendronate has been shown to be effective in reducing vertebral fractures, femoral neck fractures and extraspinal fractures. The drug significantly reduces the incidence of vertebral fractures in women at a high fracture risk (such as women with prevalent vertebral fractures) as well as in women at a low fracture risk (such as women with osteopenia) .

- Risedronate is used at a dose of 35 mg once weekly or 5 mg daily. The drug significantly reduces the incidence of vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. Risedronate has been shown to be effective in reducing the incidence of proximal femoral fractures in women at a high fracture risk (low bone mineral density, prevalent vertebral fractures), although no such efficacy has been demonstrated in women with clinical fracture risk factors only (without reduced BMD).

- Ibandronate may be given orally (150 mg once a month) or intravenously (3 mg every 3 months). The less frequent oral dosing of the drug compared with the other bisphosphonates may further increase patient compliance. Its antifracture efficacy at these doses seems to be similar to that of other bisphosphonates, although this hypothesis is only based on comparative studies of changes of BMD and bone turnover markers and has not been confirmed in large clinical studies evaluating approved doses of the drug.

- Zoledronate used at the dose of 5 mg IV every 12 months significantly reduces the risk of all types of osteoporotic fractures.

- Strontium ranelate, in addition to its antiresorptive effects, demonstrates proanabolic (osteogenic) actions. It also shows antifracture efficacy in all types of osteoporotic fractures, both vertebral and nonvertebral. It significantly reduces the incidence of femoral fractures in older women with low bone mineral density. The antifracture efficacy has been confirmed in five-year trials.

- Hormone therapy with oestrogens and progesterone prevents osteoporosis and fractures in the early postmenopausal women. Osteoporosis is not the principal indication for hormone therapy in postmenopausal women.

- Raloxifene shows antifracture efficacy only with respect to vertebral fractures. One should not expect any considerable increases in bone mineral density during treatment with raloxifene. Extraskeletal actions of the drug are of greater importance here. Not only does raloxifene not increase the risk of breast cancer, but it reduces it quite significantly. The drug also reduces LDL-cholesterol levels.

- Salmon calcitonin nasal spray (at the dose of 200 IU/day) significantly reduces the incidence of vertebral fractures without affecting the incidence nonvertebral fractures. No objective data are available on antifracture efficacy of injectable calcitonin. The drug also demonstrates specific analgesic effects.

- Teriparatide is highly effective in reducing the risk of osteoporotic fractures of any type in patients with severe osteoporosis. For safety reasons, however, the duration of treatment has been restricted to 18 months (FDA, USA) or 24 months (EMEA, European Union). In order to maintain the achieved therapeutic effects continuation of treatment with bisphosphonates should be considered.

Table 13. Adverse reactions and contraindications to drug treatment of osteoporosis		
Drug (trade name)	**Common adverse reactions**	**Contraindications**
Alendronate (Fosamax, Ostemax, Ostenil, Ostolek, Alendronat)*	Heartburn, abdominal pain Nausea Diarrhoea	Structural changes in the oesophagus and functional swallowing abnormalities Inability to remain in the upright position for 30 minutes Hypersensitivity to the drug Women of childbearing age Renal failure
Risedronate (Actonel)*	Heartburn, abdominal pain Hypertension Arthralgia	Structural changes in the oesophagus and functional swallowing abnormalities Inability to remain in the upright position for 30 minutes Hypersensitivity to the drug Women of childbearing age Renal failure
Ibandronate (Bonviva)*	Heartburn, abdominal pain Nausea Diarrhoea	Structural changes in the oesophagus and functional swallowing abnormalities Inability to remain in the upright position for 30 minutes Hypersensitivity to the drug Women of childbearing age Renal failure
Raloxifene (Evista)*	Climacteric symptoms (hot flushes, profuse sweating) Leg cramps Increased risk of thromboembolism	Presence or a history of thromboembolism Hypersensitivity to the drug Women of childbearing age Renal failure
Nasal calcitonin (Miacalcic, Tonocalcin)	Rhinitis Dry nose Nosebleeds	Hypersensitivity to the drug Women of childbearing age
Teriparatide (Forsteo)	Nausea Vertigo Leg cramps	Hypersensitivity to the drug Hypercalcaemia Severe renal failure Presence or a history of bone metastases or bone cancer Patients at increased risk of osteosarcoma who should not be treated with teriparatide: Paget's disease Unexplained elevations of alkaline phosphatase Prior external beam or implant radiotherapy to the skeleton
Strontium ranelate (Protelos)	Nausea Diarrhoea Headache	Hypersensitivity to the drug Severe renal failure Caution is advised in thromboembolism Women of childbearing age
* During administration of bisphosphonates to patients undergoing cancer treatment rare cases of jaw osteonecrosis (painful bone defect that failed to heal) were reported. To date this complication has been reported during treatment of osteoporosis in two cases. Sanitation of the oral cavity is recommended as a precaution prior to the initiation of long-term bisphosphonate treatment.		

RECOMMENDATION 7. COMBINING DRUGS

- **Combining anticatabolic drugs**

  Addition of bisphosphonates (alendronate, risedronate) to long-term hormone therapy in postmenopausal women results in a greater increase of bone mineral density. Alendronate increases BMD by 3% at 2 years in women receiving hormone therapy. Co-administration of calcitonin and oestrogens, raloxifene and alendronate also increases BMD, although the effect of this treatment on the risk of fractures has not been investigated. Due to the increased treatment costs, multiplication of potential side effects and the lack of data on the potential superiority of combined use of antiresorptive drugs, this treatment is not recommended.

- **Treatment with teriparatide and anticatabolic drugs**

  Bisphosphonates used prior to or in combination with PTH preparations reduce the anabolic effect of parathormone. However, the inclusion of bisphosphonates after completion of treatment with a PTH preparation maintains the previously achieved therapeutic effect and promote further increase of BMD. Conclusions from the existing data should be drawn cautiously due to the lack of prospective studies, the small size of the study population and especially due to the lack of evaluation of the effects of anticatabolic treatment following completion of teriparatide treatment on the incidence of fractures. It seems, however, that anticatabolic treatment, which prevents bone loss after discontinuation of teriparatide, should be recommended. Oestrogens and raloxifene do not affect the efficacy of teriparatide treatment.

RECOMMENDATION 8. DURATION OF DRUG TREATMENT FOR OSTEOPOROSIS

Osteoporosis is a chronic disease requiring lifetime treatment. While the above recommendation is obvious with respect to non-pharmacological treatment and to calcium and vitamin D_3 supplementation, the duration of the recommended drug treatment seems to be limited to the periods of published data from clinical observations of individual drugs defining their long-term safety and efficacy, namely 10-12 and 7 years for bisphosphonates (alendronate and risedronate, respectively), 8 years for raloxifene and 5 years for strontium ranelate.

Hormone therapy is indicated in women directly after the menopause, however there are neither clear recommendations as to the upper limit of age for starting therapy (both calendar age or years after the menopause), nor to the recommended duration of therapy.

Regulatory authorities have clearly define the duration of treatment with teriparatide for 18 months (NIH, USA; Canada) or 24 months (EMEA, European Union). It has not been demonstrated whether splitting the treatment into shorter cycles (intermittent schedule) is superior to repeating the treatment some time after the first course (cyclical schedule). Recommendations on the duration of osteoporosis treatment are bound to change and require updates.

RECOMMENDATION 9. PLANNING OF A MONITORING AND TREATMENT PROTOCOL AND CO-OPERATION WITH THE PATIENT

As per recommendations on page 18.

RECOMMENDATION 10. NON-PHARMACOLOGICAL MANAGEMENT

Comprehensive rehabilitation and fall prevention measures (Annexes 1 and 2):

- depend on the severity of osteoporosis
- in patients over the age of 65: should be complemented by considering elimination of the risk factors for falls.

Tasks of orthopaedic surgeons: postfracture management

Orthopaedic surgeons are generally the first and frequently the only doctors looking after patients who have suffered symptomatic (clinical) fractures.

A prevalent osteoporotic fracture increases the risk of incident fracture several times, irrespective of bone mineral density (BMD) or co-existence of other risk factors.

Immediate initiation of pharmacological treatment is recommended in addition to orthopaedic management of the fracture.

Recommendations

RECOMMENDATION 1. FRACTURE MANAGEMENT

Fractures should be managed in keeping with the current standards.

RECOMMENDATION 2. CONFIRMATION OF THE DIAGNOSIS OF OSTEOPOROSIS

In each patient with symptomatic (clinical) low-trauma fracture it is necessary to confirm the diagnosis of osteoporosis or to refer the patient to an osteoporosis center.

RECOMMENDATION 3. PHARMACOLOGICAL MANAGEMENT FOLLOWING OSTEOPOROTIC FRACTURE

Pharmacotherapy of osteoporosis is recommended in all patients confirmed to have suffered an osteoporotic fracture, unless specifically contraindicated.

It is recommended to initiate drug treatment as soon as possible following the fracture. The highest efficacy in preventing a second fracture was observed when treatment was started within 1 year of the first fracture.

Intravenous bisphosphonates (ibandronate every 3 months, zoledronate 5 mg once a year) may be particularly useful in the treatment of patients immobilised as a result of vertebral fractures or hip fractures.

The analgesic effects of salmon calcitonin are useful in the early period following symptomatic (painful) vertebral fractures, which enables rapid mobilisation and rehabilitation of the patient.

RECOMMENDATION 4. POSTFRACTURE REHABILITATION

In keeping with the recommendations included in Annex 1.

RECOMMENDATION 5. NUTRITIONAL RECOMMENDATIONS

Calcium and vitamin D supplementation and other nutritional recommendations in keeping with the current studies (see *Nutritional recommendations* above).

RECOMMENDATION 6. PATIENT EDUCATION

The patient should be informed on the risks, on appropriate lifestyle, on attempts to eliminate extraskeletal risk factors for fractures and on fall prevention.

Glucocorticosteroid-induced osteoporosis

In glucocorticosteroid-induced osteoporosis, the risk of fractures increases with the daily and cumulative doses of the drug and with the duration of treatment. Given the unique features of glucocorticosteroid-induced osteoporosis, it seems justified to develop separate recommendations for management. An important role here is played by co-existing risk factors, such as prevalent fractures, hypogonadism, low calcium supply, age >50 years and the underlying disease which requires long-term glucocorticosteroid treatment. Attention is also drawn to the necessity to prevent or treat osteoporosis as soon as possible, preferably in parallel to glucocorticosteroid treatment, in keeping with the following rule: “It’s never too early or too late to treat”. The best course of action is to reduce the dose of the glucocorticosteroid and duration of treatment to the minimum defined by clinical effectiveness and to properly treat the underlying disease.

Recommendations

RECOMMENDATION 1. DIAGNOSTIC EVALUATION AND PREVENTIVE MEASURES

This is applicable to all patients receiving systemic glucocorticosteroids at the daily dose of ≥5 mg of prednisone or equivalent for more than 3 months, especially if other risk factors for fractures are present (such as rheumatoid arthritis, postmenopause). A routine measurement of the patient's height and rib-to-hip distance once a month during glucocorticosteroid treatment is recommended.

RECOMMENDATION 2. DXA DENSITOMETRY

Central densitometry is recommended in patients prior to or in the early phase of glucocorticosteroid treatment (at the daily dose of >5 mg of prednisone or equivalent for >3 months). Monitoring of BMD changes during treatment is recommended every 6-12 months.

RECOMMENDATION 3. CALCIUM AND VITAMIN D SUPPLEMENTATION

Calcium and vitamin D supplementation is the mainstay of prevention in all patients scheduled for or undergoing treatment with prednisone, or equivalent, at the daily dose of ≥5 mg for more than 3 months. The daily supply of elemental calcium, having considered dietary intake, should be 1000-1500 mg and vitamin D (or alpha-calcidiol) should be provided at 800 IU/day.

RECOMMENDATION 4. QUALIFICATION FOR PHARMACOLOGICAL TREATMENT

This recommendation applies to the following patients receiving long-term glucocorticosteroid treatment:

- All the patients with confirmed osteoporotic fracture (even without performing DXA measurements).
- Patients with a moderate absolute fracture risk (10-20%) calculated according to sex, age and BMD (see *Recommendations for doctors at osteoporosis outpatient clinics* above).
- Demonstration of BMD Z-score below -1.5 SD according to sex and age in premenopausal women and men below 50 years of age is a basis for therapeutic intervention.

RECOMMENDATION 5. NON-PHARMACOLOGICAL MANAGEMENT OF GLUCOCORTICOSTEROID-INDUCED OSTEOPOROSIS

- Lifestyle modification and modification of the other risk factors.
- Rehabilitation in patients receiving long-term glucocorticosteroid treatment depends on the following factors:
- dose of prednisone and duration of treatment
- functional deficit and systemic capabilities related to the underlying disease.

RECOMMENDATION 6. PHARMACOLOGICAL MANAGEMENT OF GLUCOCORTICOSTEROID-INDUCED OSTEOPOROSIS

- In most cases it is justified to use calcium (up to 1500 mg/day) and vitamin D (800-1000 IU) as supplementary treatment or in order to prevent osteoporosis.

- Bisphosphonates: alendronate and risedronate significantly reduce the incidence of fractures in men and women managed with glucocorticosteroids. Because no data are available on the effects of maternal treatment with bisphosphonates on foetal development, the use of bisphosphonates in women of childbearing age should be considered on an individual basis. Using other

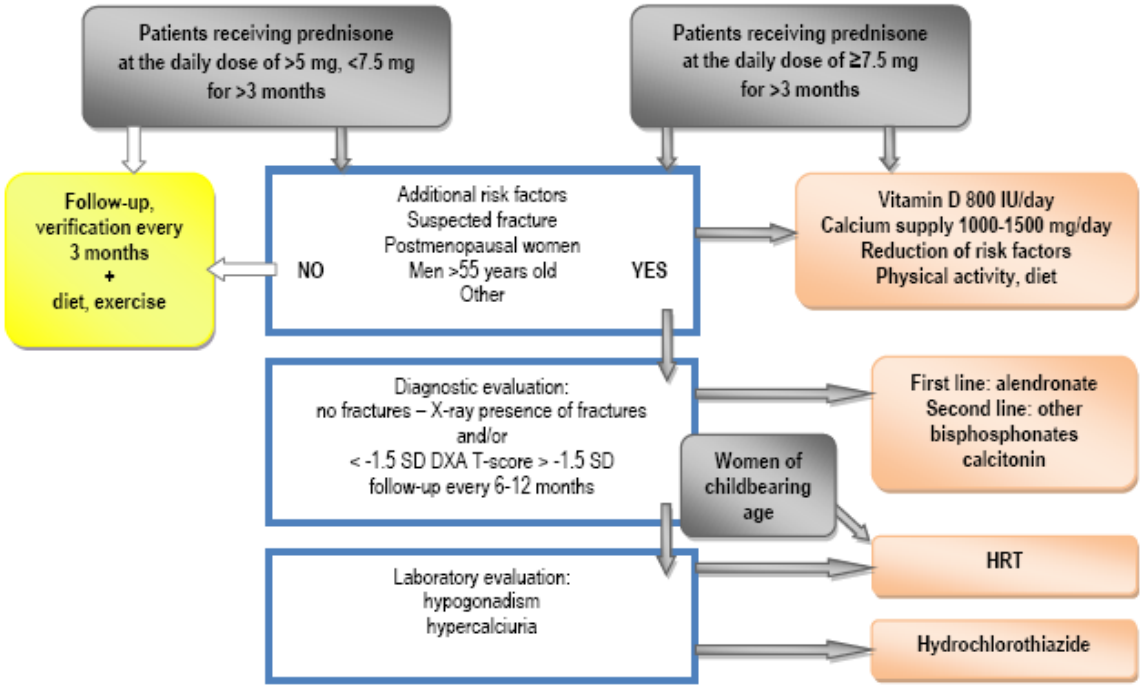
bisphosphonates, including intravenous bisphosphonates (such as ibandronate), may be considered in special situations as second-line treatment.

- While calcitonin in the form of injections or nasal spray reduces vertebral bone loss in patients receiving glucocorticosteroids, its antifracture efficacy has not been demonstrated in these patients. Use of calcitonin may be considered as a second-line treatment only in those patients in whom bisphosphonates cannot be used or directly following recent fractures, taking advantage of its analgesic action.

- Hormone therapy with oestrogen in women and testosterone in men with hypogonadism should be treated as an complementary measure in the drug treatment of steroid-induced osteoporosis aimed at preventing bone and muscle loss and improving the quality of life.

- Teriparatide is very likely to be used as a second-line treatment in severe glucocorticosteroid-induced osteoporosis. Its use may be considered in exceptional severe cases as an unconventional measure.

Figure 2. Algorithm for the management of glucocorticosteroid-induced osteoporosis

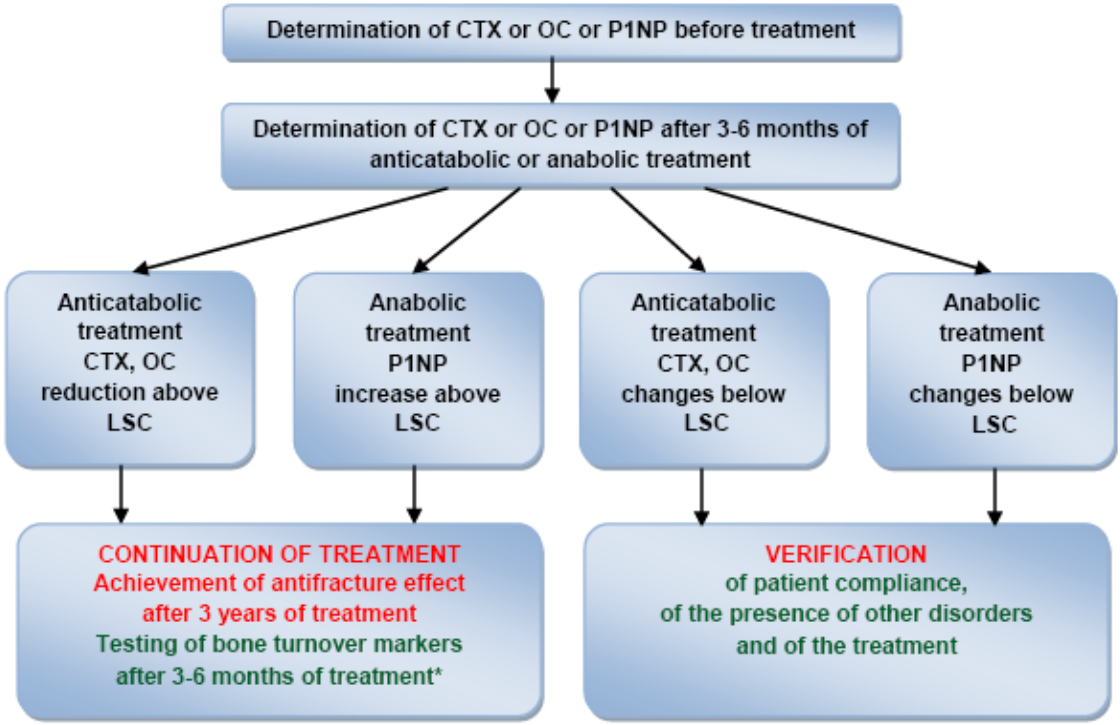


Treatment optimisation: tasks of general practitioners and other specialist doctors

Ensuring persistence on treatment and patient compliance are essential for treatment costs and efficacy. These goals are achieved through short- and long-term monitoring of treatment. Bone turnover markers (CTX, P1NP, OC) are used to assess the efficacy of anticatabolic (bisphosphonates, raloxifene, hormone therapy, calcitonin) and anabolic (PTH) treatment in the short term (at 3 months). Long-term assessment of efficacy is based on the measurement of bone mass (BMD) by densitometry (anticatabolic, anabolic and mixed-action drugs). Changes in bone

metabolism at 3 months and BMD increases at 1 year have been demonstrated to positively correlate with the antifracture effect.

Figure 3. Algorithm for osteoporosis management monitoring with the use of bone turnover markers



* Due to the dynamics of changes, it is recommended to determine CTX at 3 months and OC and P1NP at 6 months.

RECOMMENDATION 1. TREATMENT MONITORING BY BONE TURNOVER MARKERS

- **Principles of the interpretation of results**

  Interpretation of results is based on the least significant change (LSC) method which is used to determine whether the observed change in the concentrations of bone turnover markers is an actual change translating into a new metabolic balance rather than being a purely random change. Exceeding the LSC value suggests that the treatment is effective. LSC values for the individual bone turnover markers are as follows: 44% for CTX, 25% for P1NP and 15% for OC (for the automated method on the Elecsys system).

- **Interpretation of results**

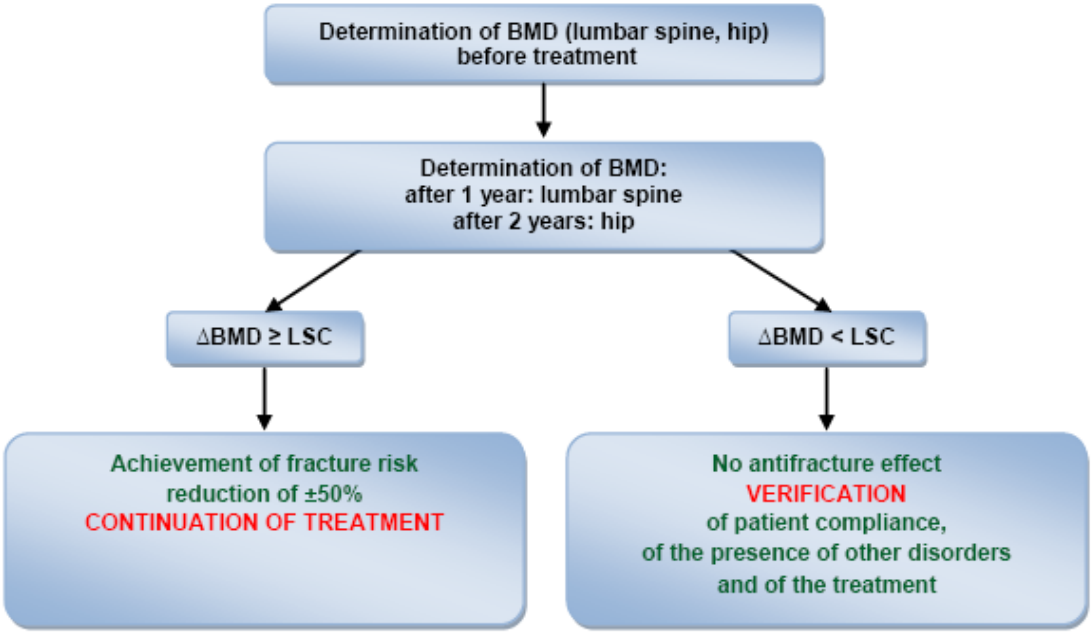
  Treatment efficacy and patient compliance are evidenced by th following changes:

a. For anticatabolic treatment: A **reduction** of the marker level above LSC.
b. For anabolic treatment: An **increase** of the marker level above LSC.

  Relevant actions to be taken are summarised in Algorithm 4 (Figure 2).

- The concentrations of bone turnover markers are determined in the serum obtained from venous blood collected under fasting conditions between 7 and 10 in the morning. In the case of an incident fracture blood is collected within 12 hours of the fracture.

Figure 4. Algorithm for osteoporosis management monitoring with the use of densitometry



RECOMMENDATION 2. TREATMENT MONITORING BY DENSITOMETRY

- **Principles of the interpretation of results**

Interpretation of BMD changes during treatment monitoring requires quality control of the measurements involving determination of the following parameters:

- reproducibility error
- least significant change (LSC).

Determination of the reproducibility error enables a comparison of subsequent measurements during treatment.

Determination of the reproducibility error, which is laboratory-specific, requires performance of three measurements in 14 patients with repositioning or two measurements in 27 patients with repositioning. The reproducibility error is expressed in absolute values (g/cm^2) or as the coefficient of variation (CV) in percent (absolute error/mean × 100%).

The lowest significant change of LSC serves to establish whether the observed change in BMD with time represents an actual or random change. It is a requirement that the difference observed between the baseline and subsequent test exceeds LSC calculated from the following formula:

$$LSC = 2.8 \times \text{reproducibility error}$$

- **Interpretation of results**

The algorithm of treatment monitoring based in BMD with the use of LSC is presented in Algorithm 6 (Figure 3). BMD changes greater than or equal to LSC indicate treatment efficacy.

RECOMMENDATION 3. FAILURE TO RESPOND TO TREATMENT

Please refer to Figures 2 and 3. The following should be analysed:

- Compliance with dosage recommendations.

- Presence of co-morbidities, vitamin D deficiency, calcium deficiency.
- Switching to alternative treatment with a different mechanism of action.

Osteoporosis in young women with hypoestrogenism

Prevention and treatment of osteoporosis in young women is a very important issue in gynaecological endocrinology. The fundamental goal is to achieve an optimum peak bone mass and to prevent its loss. Attention should be paid to diet, physical exercise and first of all to treatment of menstruation abnormalities associated with hypoestrogenism. Dietary recommendations focus on meeting the dietary requirements for calcium and vitamin D_3. In cases of insufficient dietary calcium supply, supplementation of this element should be considered. The same applies to vitamin D_3.

Table 14. Clinical conditions characterised by hypoestrogenism and the risk of osteoporosis

Pathogenesis	Examples
Hypothalamo-pituitary insufficiency	Amenorrhoea associated with weight loss Amenorrhoea associated with excessive physical exertion Amenorrhoea associated with stress
Hyperprolactinaemia	
Primary ovarian failure	Gonadal dysgenesis Ovarian hypoplasia Premature ovarian failure
Iatrogenic causes	Prior chemo- and/or radiotherapy Surgical castration

Recommendations

RECOMMENDATION 1. IDENTIFICATION OF PATIENTS

Identification of patients with hypoestrogenism and the risk of osteoporosis (Table 14).

RECOMMENDATION 2. INDICATIONS FOR DENSITOMETRY

Secondary amenorrhoea of more than 6 months' duration in women below 45 years of age is an indication for densitometry (after pregnancy has been ruled out!).

RECOMMENDATION 3. TREATMENT OF MENSTRUAL ABNORMALITIES

The main goal of treatment of menstrual abnormalities is to prevent low oestradiol levels in the body. Cyclical administration of natural oestrogens with the addition of a progestagen in the second phase of the menstrual cycle is recommended.

Hormonal contraceptive pills should not be used in the types of menstrual abnormalities listed in Table 14.

Osteoporosis in men

Thirty percent of all hip fractures occur in men. The lifetime risk of a typical osteoporotic fracture is estimated at about 13% for a 50-year-old man (versus about 30% in women). Osteoporotic fractures in men are a considerable cause of all-cause mortality and the mortality due to proximal femoral fractures in men versus women is twice as high. The causes of osteoporosis in men are similar to those observed in women.

Hypogonadism is the best documented risk factor for low BMD in men. Testosterone deficiency also leads to an increased risk of fractures. In contrast to women, in whom the menopause is a relatively abrupt process, the age-related reduction in testosterone levels in ageing men is linear. As a result, men do not experience the abrupt acceleration of bone loss. Thanks to the higher peak bone mass and the greater periosteal apposition effect than those seen in women men experience osteoporotic fractures in a more advanced age.

Recommendations

RECOMMENDATION 1. DENSITOMETRY

Central densitometry should be recommended in all men over the age of 70 with clinical risk factors for fractures or a loss of height of 2 cm or more.

In each case of height reduction by more than 4 cm or considerable kyphosis lateral spine X-ray is recommended to rule out occult vertebral fractures.

RECOMMENDATION 2. COMPREHENSIVE PREVENTION OF FRACTURES

Comprehensive prevention of fractures applies to all men over the age of 65. Patient education should focus on the presentation of risks, on lifestyle and diet advice, on elimination of extraskeletal risk factors for fractures and on the prevention of falls.

RECOMMENDATION 3. NUTRITIONAL RECOMMENDATIONS

Nutritional recommendations in keeping with the current studies (see *Nutritional recommendations* above).

RECOMMENDATION 4. CRITERIA FOR INITIATING DRUG TREATMENT

Drug treatment for osteoporosis should first of all be offered to men with a diagnosed osteoporotic fracture and all men at a high 10-year absolute fracture risk calculated from age and bone mineral density.

RECOMMENDATION 5. FUNCTIONAL IMPROVEMENT

Functional improvement and physical therapy (in co-operation with a specialist in medical rehabilitation and a physiotherapist) as well as fall prevention should include all men over the age of 65 irrespective of fracture risk and all patients with prevalent osteoporotic fractures irrespective of age.

RECOMMENDATION 6. PRINCIPLES OF PHARMACOLOGICAL MANAGEMENT IN MEN

- Testosterone treatment increases bone mineral density only in men with hypogonadism. It is unknown whether testosterone supplementation affects the risk of fractures.
- Alendronate prevents osteoporotic fractures in men irrespective of the hormonal status.
- Risedronate and teriparatide increase bone mass in men with osteoporosis.

Osteoporosis and diabetes mellitus

Diabetes mellitus and the related metabolic abnormalities lead to significant changes in bone metabolism and increase the risk of fractures. Impaired bone formation and relatively increased bone resorption resulting from the deficiency of insulin and IGF-1 are characteristic of type 1 diabetes, which leads to impaired bone formation and lower peak bone mass. In type 2 diabetes, despite the increased bone formation (hyperinsulinism leads to increased bone formation) an increased risk of fractures, especially peripheral is observed. The common pathogenetic elements in both types of diabetes include: lower quality and strength of bone and the negative calcium balance resulting from insufficient dietary supply of calcium (limited consumption of milk), impaired intestinal absorption and hypercalciuria secondary to hyperglycaemia.

Local osteoporosis and fractures are characteristic of diabetes mellitus. The risk of fractures of feet bones is proportionate to the degree of obesity and neuropathy.

Recommendations

RECOMMENDATION 1. FUNDAMENTAL ACTION

It is recommended to control diabetes (HbA_{1c} ≤6.5%) and include information on bone complications in the patient education programme on diabetes (screening, lifestyle, physical activity).

RECOMMENDATION 2. DIAGNOSTIC RECOMMENDATIONS

Screening is recommended in patients with type 1 diabetes of long duration and in lean women with complications of type 2 diabetes. If generalised bone loss is observed in type 2 diabetes, the patient should be started on insulin to take advantage of the drug's anabolic effects on bone.

RECOMMENDATION 3. NUTRITIONAL RECOMMENDATIONS

Routine supplementation of calcium (1000-1500 mg/day) and vitamin D (800-2000 IU/day) is necessary (the diet in diabetes is characterised by low calcium supply resulting from restricted intake of dairy products).

RECOMMENDATION 4. TREATMENT RECOMMENDATIONS

Early management of osteoporosis in diabetes is recommended (calcium and vitamin D supplements, bisphosphonates). The National Osteoporosis Foundation (NOF) recommends a BMD T-score of < -1.5 SD as the threshold of intervention aimed to reduce the risk of fractures in diabetes.

Abnormalities of calcium and phosphate metabolism and bone metabolism in patients with chronic kidney disease

The complex nature of calcium and phosphate metabolism abnormalities and differentiation between the various forms of bone changes in the individual types of renal osteodystrophy require a comprehensive biochemical assessment and, in some cases, bone biopsy with histomorphometric evaluation. For detailed management guidelines in these cases please refer to the Recommendations of the National Nephrology Consultant Working Group.

Annexes

ANNEX 1
PRINCIPLES OF REHABILITATION IN OSTEOPOROSIS

I. Low to moderate fracture risk

History
Risk factors for fractures (Table 1)

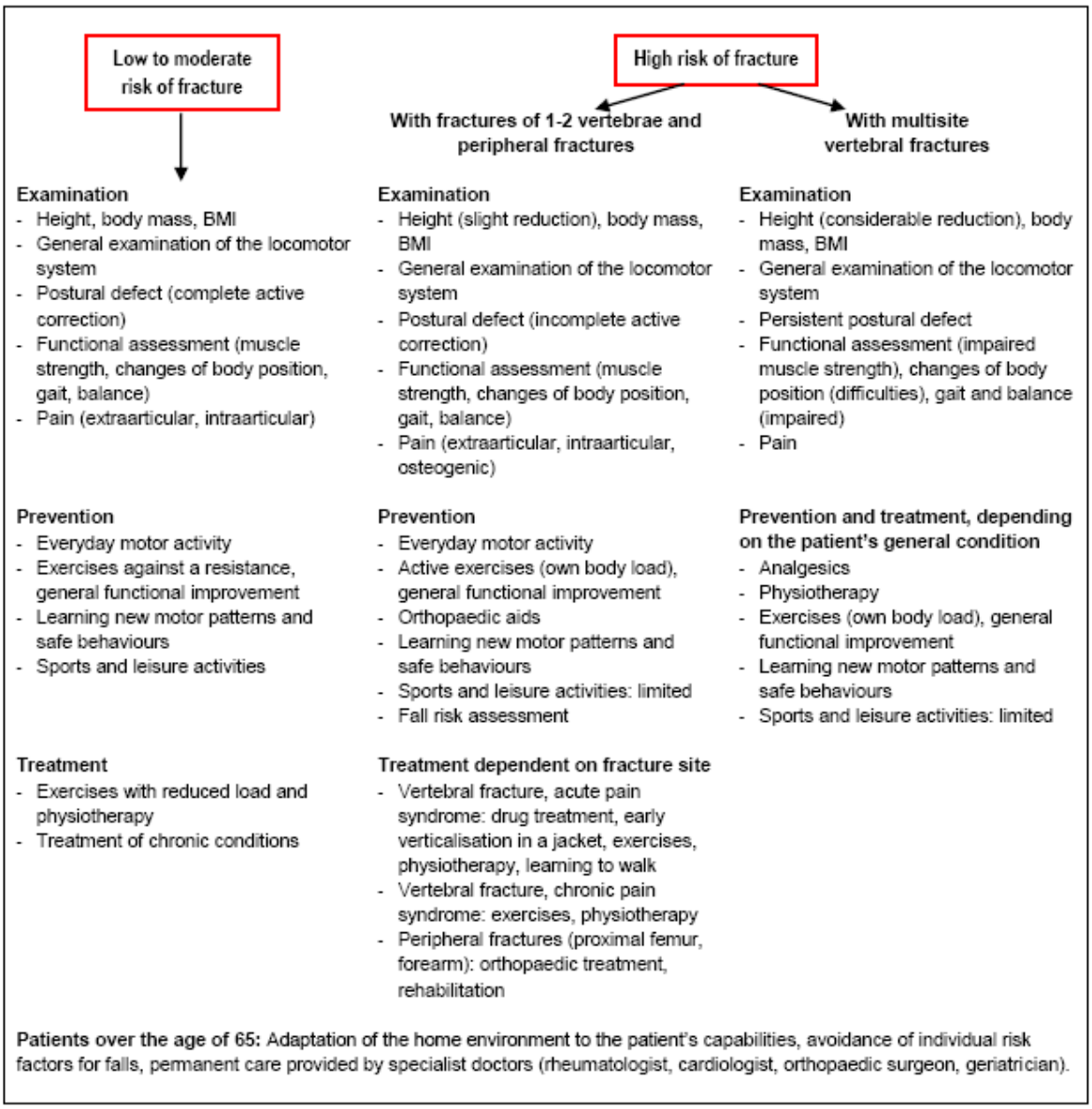
Physical examination
- Height (assessment of height reduction), body mass index (BMI)
- Locomotor system
- General examination of the locomotor system (assessment of degenerative changes in the peripheral joints and the spine)
- Assessment of posture (assessment of active correction: complete vs incomplete) and muscle status (paravertebral, abdominal and gluteal muscles)
- Pain: extraarticular (tenderness of paravertebral muscles), intraarticular (on extreme movements of the spine), intercostal (on maximum inspiration)
- Functional assessment of the following: general muscle strength, position changes, gait, balance

Prevention
- Everyday motor activity
- Exercises aimed to correct the posture
- Exercises aimed to improve muscle strength (with own body load: isometric exercises), resistance exercises for the upper and lower extremities
- Exercises improving overall function: balance, co-ordination, flexibility, breathing and relaxation exercises
- Learning to safely perform activities of daily living according to new motor patterns (elimination of spinal flexion and rotation) and learning safe behaviours (safe fall)
- Sports and leisure activities

Treatment
- Analgesic treatment: Exercises with reduced weight load (swimming pool), physiotherapy
- Specific rehabilitation management in the treatment of chronic diseases which are an important cause of reduced motor capabilities:
- Disorders of the locomotor system (osteoarthritis, inflammatory rheumatic diseases): rehabilitation, orthopaedic devices, surgery
- Neurological disorders
- Cardiovascular disorders
- Metabolic disorders
- Psychiatric disorders (depression, anorexia)

Additionally, in patients over the age of 65:
- Identification and elimination of individual risk factors for falls (modification of drug treatment, correction of visual and hearing problems) and of external factors (adjustment of the patient's home environment to his/her capabilities)
- Specialist care (e.g. neurologist, cardiologist)
- Education on safe behaviours

Figure 5. Algorithm for comprehensive rehabilitation in osteoporosis



II. High fracture risk (no fractures, fractures of 1-2 vertebrae and peripheral fractures)

All the above plus the following:

Prevention

- Active exercises aimed to improve muscle strength in the upper and lower extremities, improvement of movement ranges in the peripheral joints (with own body load)
- At least one-hour walk every day
- Orthopaedic devices (as required): walking frames, crutches, support collars, jacket, back stabiliser, clavicular stabiliser, hip shield
- Sports and leisure activities matching the patient's functional capabilities (sports associated with the risk of loss of balance and fall are prohibited)

Treatment

- Analgesics
- At the fracture site

- Early period: in keeping with postoperative standards
- Late period: depending on the resulting dysfunction

- **Depending on the patient's general condition, exercises aimed to improve overall function, physiotherapy.**

ANNEX 2
FALL PREVENTION STRATEGY

Due to the high cost this intervention is recommended in selected groups of patients at high risk for falls:

- patients with gait and balance abnormalities or other identified risk factors
- patients with a history of falls, especially multiple falls
- patients over 80 years of age.

The fall prevention strategy involves:

- **Preventive measures in the entire elderly population**
  - Health education
  - Promotion of motor activity exceeding the activities of daily living as a factor that prevents bone and muscle loss, ensuring preservation of fitness and mobility
  - Education on the risk of falls and injuries, making patients aware of the internal and external risk factors and of the ways they can reduce the risk of falls
  - Counteracting individual risk factors

- **Identification of high-risk groups**
  - Elicitation of the history of falls in all elderly patients using the services of a healthcare facility (medical consultations, rehabilitation, community nurse visits): at least once a year.
  - Patients reporting a one-off fall: Performance of the "get up and go" test (or another screening test) to detect any balance or gait abnormalities, instability; if these are detected, the patient should be referred to a specialist (geriatrician , rheumatologist, orthopaedic surgeon) for a full assessment of falls and development of subsequent intervention.
  - All patients with a history of multiple falls should be referred for a full assessment of the risk of falls and implementation of appropriate intervention.

- **Assessment of the risk of falls**
  - History focused on the circumstances and location of the fall
  - General medical history and physical examination (plus laboratory tests, imaging studies and specialist consultations, as necessary) aimed to establish:
    - nature of the current illness (acute, chronic)
    - current medication (types and doses)
    - individual risk factors and factors predisposing to falls (individual risk)
  - Assessment of functional capability, muscle strength, necessity to use technical aids
  - Neurological assessment and assessment of the senses (vision, proprioception)
  - Environmental risk assessment

- **Implementation of the necessary interventions**
  - Guided by the identified risk factors
  - Modification of pharmacological treatment using the lowest possible number of drugs at the lowest effective doses; in particular, sedatives and hypnotics should be discontinued, antihypertensive, dehydration and antidepressant treatments should be monitored, long-acting drugs that do not cause rapid changes of blood concentrations should be used.

- Motor rehabilitation (the duration, frequency and intensity of exercises are of essence), progressive exercise load, taking contraindications into account:
  - increasing muscle mass: exercises against a resistance
  - dynamic endurance exercises
  - balance exercises
  - gait exercises
  - transfer
  - exercises aimed to increase the range of movements of the lower extremities
  - posture exercises
  - exercises involving performance of everyday activities
- Modification of the patient's environment in order to eliminate environmental risk factors (anti-skidding mats, grips, banisters, stable furniture, lighting)
- Education and advice on safe behaviours
- Treatment, as necessary, of such conditions as: arrhythmia, diseases of the locomotor system, vision disorders, postural hypotension etc.
- Vitamin D directly affects the neuromuscular system, which translates into increased muscle strength and improved balance, increased speed of gait, smoother performance of functional tests, but first of all reduced risk of falls (see *Nutritional recommendations* above).

ANNEX 3
METHODOLOGY OF THE ANALYSIS OF EVIDENCE LEVELS AND GRADES OF RECOMMENDATION

Please refer to Tables 15 and 16.

Table 15. Grades of recommendation according to the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk)

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population OR A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results OR Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results OR Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 OR Extrapolated evidence from studies rated as 2+

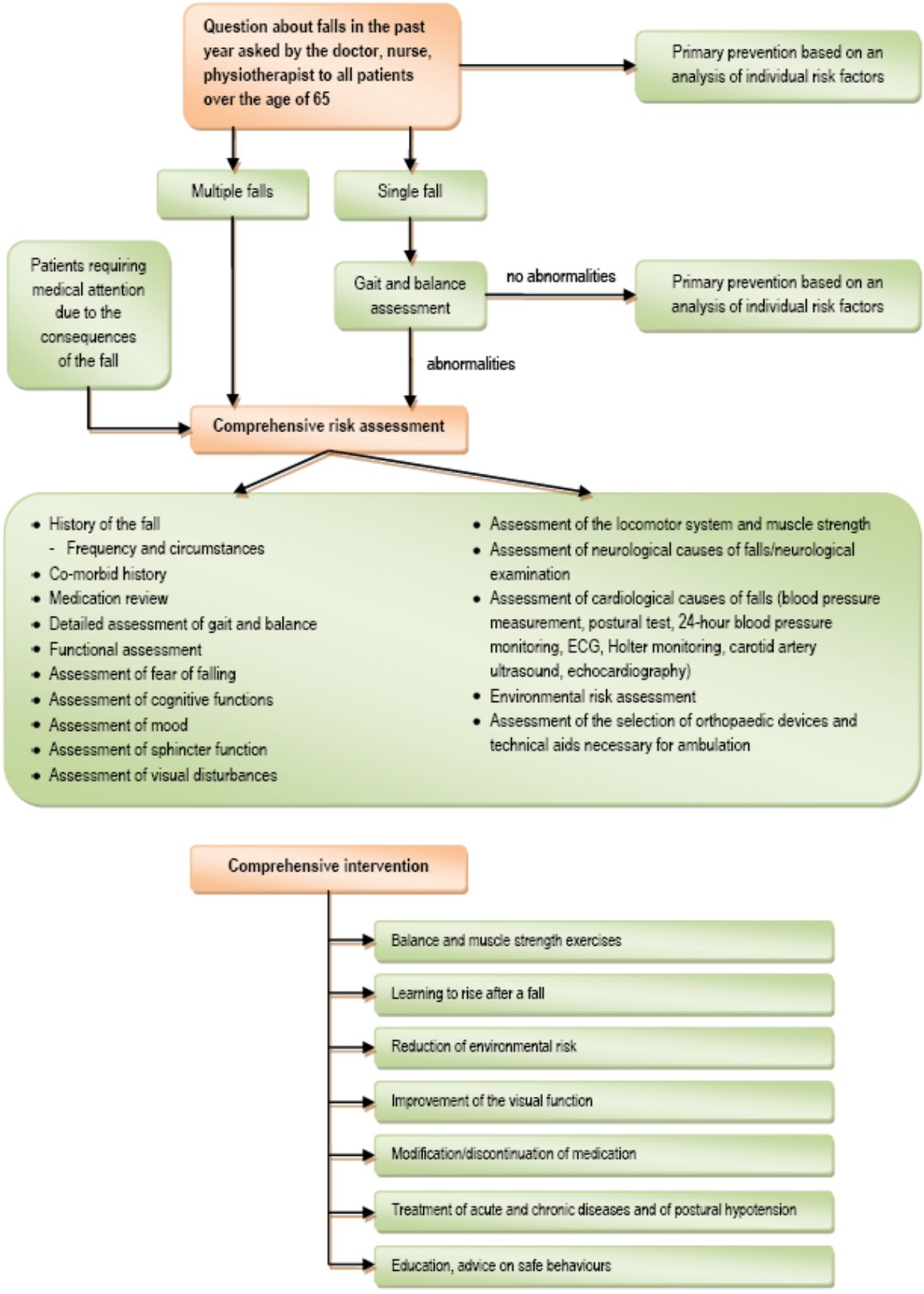
Table 16. Levels of evidence according to the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk)	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2–	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

ANNEX 4
INFORMATION FOR HEALTHCARE PROVIDERS

Data on fractures and fracture treatment costs in Poland and in Europe

Estimates of the National Health Fund in Poland document approximately 30,000 cases of hip fracture and 150,000 cases of fractures in all sites annually. The current annual fracture treatment costs in the European Union amount to €14,000 per hip fracture, €12,000 per vertebral fracture and €2,000 per each Colles' fracture. Using the National Health Fund data for the Mazowieckie Province and Polish epidemiological data for the year 2005 the annual incidence of hip fracture in Poland was estimated at 27,434 (7,970 in men and 19,464 in women). Due to the projected rise in the average life expectancy among Poles, the number of these fractures may considerably increase in the coming years. The incidence rates of hip fractures in women and men at the age of 80 in Poland are comparable to those in Italy and Canada. They are lower than those in Sweden, Czech Republic, Germany and Slovakia, but higher than those in France, Spain and Portugal. The 10-year fracture risk is 9.2% in women at the age of 80 and 4.9% in men of the same age. In Finland and Canada (specifically Ontario) a reduction has been reported in the incidence of hip fractures by 17% between 1995 and 2005 (Finland) and by 10% between 2003 and 2005 (Canada), which is partially explained by the comprehensive antifracture measures in those countries.

Figure 6. Algorithm for the risk assessment and prevention of falls in patients over 65 years of age.



Pharmacoeconomic analyses in osteoporosis in Poland and other countries of the world

An effective medical intervention aimed at reducing the number of osteoporotic fractures consists of effective diagnostic and treatment strategies. Pharmacoeconomic analyses performed in developed countries have demonstrated cost-effectiveness of diagnostic strategies based on BMD, diagnostic evaluation of asymptomatic vertebral fractures and on bone metabolism. Elimination of patient non-compliance in the pharmacoeconomic analysis has demonstrated superiority over classical treatment.

Because pharmacoeconomic analyses are country-specific, results obtained in other countries cannot be directly related to Poland. These studies may, however, inspire new analyses and the models they use may be adapted for the purpose of local pharmacoeconomic studies. Based on publications that appeared between 2002 and 2005, a structure of pharmacoeconomic analysis in osteoporosis has been proposed on the basis of Markov's model with the suggestion to use it for local analyses. In Poland, pharmacoeconomic analyses on alendronate, ibandronate and raloxifene have been published.

Polish osteoporosis studies

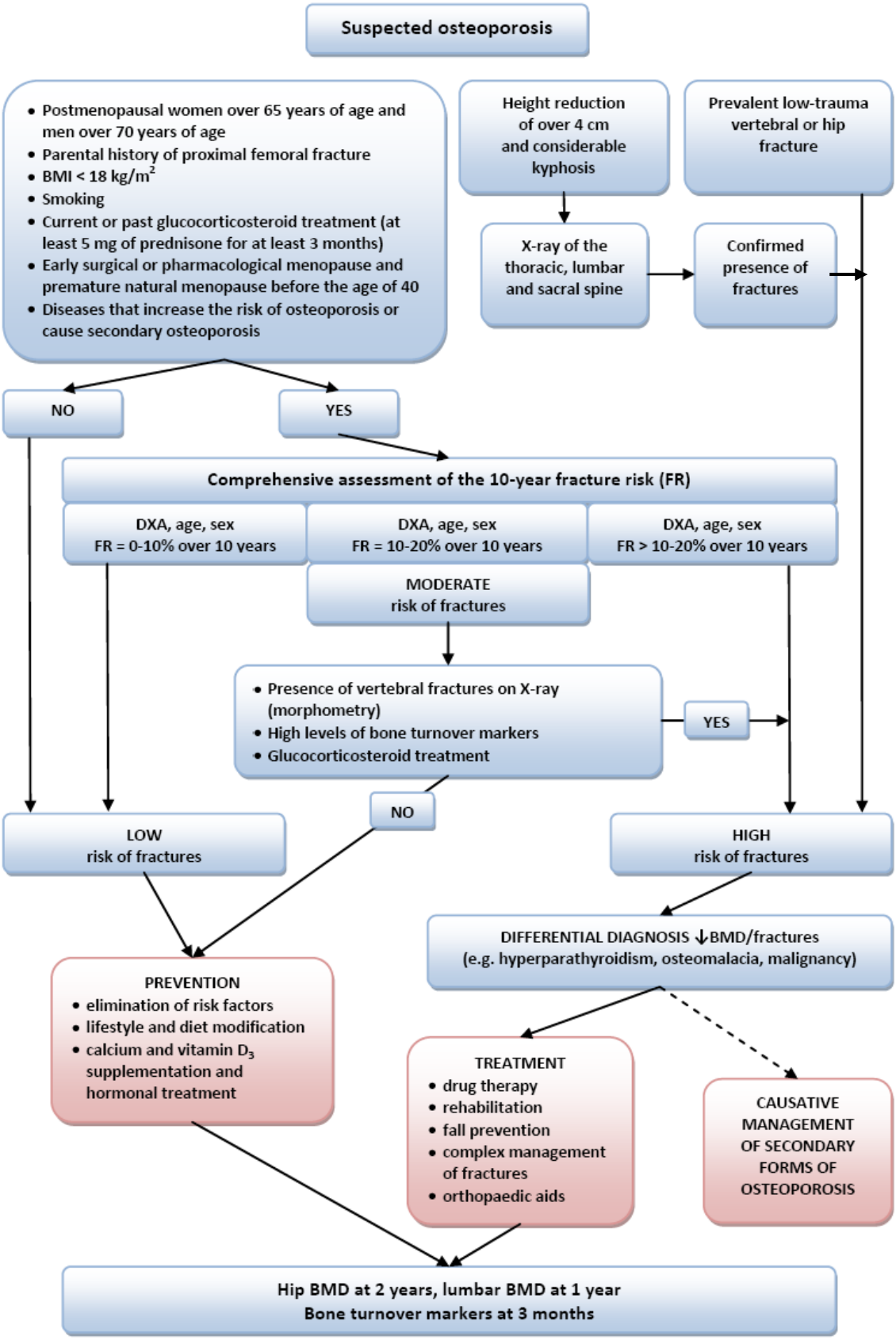
Osteoporosis studies in Poland are performed by many medical and non-medical research centres. In order to systematise organisational and educational activities related to osteoporosis in collaboration with the Ministry of Health and the State Committee for Scientific Research, one specific and two implementation programmes have been completed. The specific programme was entitled: "Early identification of risks and effective prevention of osteoporotic fractures in the Polish population: EPOLOS" (No. 4 P05D 004 98 C/3959). Thanks to the correct activities in these programmes a basis has been created for the implementation of systemic solutions to prevent of osteoporotic fractures in Poland. The genetic studies of the EPOLOS programme have been included in the European analyses in the GENOMOS system.

In collaboration with the International Osteoporosis Foundation (IOF) and the International Society for Clinical Densitometry (ISCD) (attached) the international certification system has covered doctors and operators from 9 teaching hospitals and 55 primary care facilities. Of the 389 participants, 267 doctors and operators passes the examination and was awarded the internationally-recognised "Clinical Densitometry Specialist" certificate.

As part of informational and educational activities related to the diagnosis, prevention and treatment of osteoporosis and intended for doctors and operators, many books and textbooks have been published and quality management principles in densitometric assessments under the internal and external audit systems have been established. As part of the internal audit a certification course was organised for operators of densitometers entitled: "Safety standards and principles of GLP (Good Laboratory Practice) in skeletal system densitometry".

As part of the implementation of the external audit system, the principles of quality management in densitometry laboratories have been established and quality control of densitometry assessments has been performed at 10 centres using 2 types of phantoms. Awareness campaigns also included patients. The Healthy Bone Enthusiasts Society (STENKO) is a centre that focuses on patient education in the field of fracture prevention and healthy lifestyle promotion.

GENERAL ALGORITHM OF OSTEOPOROSIS MANAGEMENT (M80/M81)



ALGORITHM OF DRUG MANAGEMENT IN OSTEOPOROSIS

1.
Rule out secondary causes of low bone mass and low-trauma fractures

2.
Calcium and vitamin D_3 supplements
Calcium: 1000 mg/day, vitamin D_3: 800-1000 IU/day

	LEVEL OF EVIDENCE		
	VERTEBRAE	PROXIMAL FEMUR	↑BMD

3.
Treatment of choice

Bisphosphonates are recommended as the treatment of choice for the prevention of osteoporotic fractures in:
1. Patients with prevalent low-trauma vertebral or hip fractures: without the need for DXA
2. Patients at high 10-year fracture risk (>20%)
3. Patients at moderate 10-year fracture risk (10-20%) and:
   - asymptomatic spina fracture on VFA morphometry or X-ray
   - managed with glucocorticosteroids
   - high activities of bone turnover markers

ALENDRONATE 70 mg/week (or 10 mg/day)	[A]	[A]	[A]
or			
RISEDRONATE 35 mg/week (or 5 mg/day)	[A]	[A]	[A]
or			
IBANDRONATE 150 mg/month	[A]	[B]	[A]

Strontium ranelate is an alternative recommended therapeutic option in postmenopausal women. It may be the treatment of choice in women:
1. Over the age of 80
2. With BMD values consistent with osteopenia
3. Independently of the activities of bone turnover markers

STRONTIUM RANELATE 2 g/day	[A]	[A]	[A]

4.
The other treatment options useful in patients with contraindications to the above drugs, who are unable to comply with dosing recommendations or who are intolerant of them

Intravenous bisphosphonates may enable effective treatment of patients with contraindications to oral treatment, such as immobilised patients (e.g. patients directly after vertebral or hip fractures, stroke patients), patients with gastrointestinal pathologies and patients intolerant of oral bisphosphonates.

IBANDRONATE 3 mg IV q 3 months	[A]	[A]	[A]
ZOLEDRONATE* 5 mg IV q 12 months	[A]	[B]	[A]

Raloxifene
Raloxifene demonstrates antifracture efficacy only in vertebral fractures.

RALOXIFENE 60 mg/day	[A]	[–]	[A]

Calcitonin
Calcitonin demonstrates antifracture efficacy only in vertebral fractures.

CALCITONIN 200 IU/day (1 spray) intranasal	[A]	[–]	[A]

Hormonal therapy (HT)
Hormonal therapy (based on oestrogen and progesterone) in women may prevent osteoporosis and fractures in the early postmenopausal period. Osteoporosis is not a primary indication for hormonal therapy in postmenopausal women.
Although supplementation of testosterone increases bone mineral density in men with hypogonadism, the effect of this treatment on fracture risk remains unknown.

HT (various products, various routes of administration, various dosages)	[A]	women [A]	[A]
	[–]	men [–]	[A]

Teriparatide
Highly effective in reducing the risk of osteoporotic fractures in women and men with severe osteoporosis. For safety reasons, duration of treatment has been restricted to 18 (FDA, USA) or 24 (EMEA, European Union) months. Maintenance of therapeutic effect requires continuation of treatment with a bisphosphonate.

TERIPARATIDE 20 µg/day (SC)	[A]	[–]	[A]

* Expected date of regulatory approval (at the time of printing): September 2007.

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