DIFFERENTIAL TREATMENT OF OSTEOPOROSIS WITH MEDICAMENTS

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DEFINITION AND CLASSIFICATION

In the past, the term osteoporosis was used for manifest osteoporosis presenting with low bone mass and fractures. After consensus-conferences in the years 1991 and 1993 [1] osteoporosis is also the status of low bone mineral density with an increased risk for fractures – thus, the definition of osteoporosis of today is that of a systemic skeletal-disease, characterised by diminished bone mass and impairment of the micro-architecture of the skeletal tissue leading to increased fragility, e.g. an increased risk of fractures. Now the definition of osteoporosis without fractures is less precise. It depends on arbitrary limits of osteodensitometrical values. It is consensus to name the situation of BMD-values lower –2.5 standard-deviations below the mean of young healthy adults (30 years) "osteoporosis", this is the so called T-value. The dilemma of this definition is evident for people of 80 years of age: about 80 % of them are "osteoporotic" without any proof that they all need treatment. Therefore, especially in the aged population it is justified to relate the individual BMD-value to the mean value of the age-group (Z-value). This could help to avoid blind over-treatment.

This chapter deals with the drug treatment of manifest osteoporosis (presenting with fractures), a condition with an absolute indication for treatment. Depending on the individual risk-situation these recommendations can be transferred to situations of lower bone mass (osteopenia), e. g. the range between –1 and –2.5 standard-deviations (T-value), and to osteoporosis (–2.5 SD T-value) without fractures.

The origin of osteoporosis can be primary or idiopathic – in those cases no leading risk factor or causal factor is evident. As a rule, postmenopausal osteoporosis in women also is defined as "idiopathic", although the typical bone loss after the menopause contributes. The reason for the term idiopathic is the fact that all women pass the menopause, but only part of them (20 %? more?) develop osteoporosis.

Secondary osteoporoses (table 1) present with a leading risk or cause, for example hypogonadism in men, hypogonadism before the age-period of the menopause in women (when estrogens normally are still produced), endocrinopathies like hypercortisolism, hyperparathyroidism and others.

PRINCIPLES OF DRUG TREATMENT OF OSTEOPOROSIS

Medicinal treatment is complicated and pretentious. Therefore only the medical

doctor should start treatment who is willing to invest the necessary time for the patient and who acquired the respective expertise. In contrast to suggestive simplifications, there is no general and simple case of osteoporosis, neither is there a single drug or uniform principal therapy. Every individual patient has to be separately diagnosed in order to start afterwards individual treatment.

Before drugs are considered, principal questions regarding the contributions of lifestyle and general health condition have to be answered. Even in the case of idiopathic osteoporosis, the multifactorial origin has to be considered: If a woman's mother already suffered from osteoporosis, the daughter needs exact consultation with respect to her lifestyle in order to avoid common risk factors. Beside the family history, the case history is of utmost importance: How was nutrition with respect to calcium (and vitamin D)? How was the mean physical activity? If e.g. a woman has low bone density in spite of optimal physical activity (sports) and healthy nutrition including calcium, she has to be considered for special medical treatment for prevention of osteoporosis. If a woman with the same BMD-value was inactive and undernourished with respect to calcium, the filling-in of these defects by regular physical activity (2–3 times per week) and optimation of calcium-intake promises reasonable improvement. Switching from a low calcium-intake of only 600 mg per day to 1,000 mg and persuading an immobile person to exercise regularly, will increase bone mass and density by 5–10% in about 1–2 years. To achieve the same effect by drugs would cost a reasonable sum from the public health system which could be spared in those cases. Skipping such a history and forgetting such concepts will increase health costs for the society.

Table 1. Classification of osteoporosis

A. Idiopathic (= primary) osteoporosis
- Juvenile (both sexes)
- Premenopausal
- Postmenopausal type I (trabecular bone: spine fracture)
- Postmenopausal type II (compact bone: hip fracture)
- Male (adult)

B. Secondary osteoporosis

1. Endocrinopathy
- Hypogonadism
- Hypercortisolism (endogenous, exogenous)
- Thyreotoxicosis
- Hyperparathyreoidism

2. Within complex osteopathies:
- Gastrointestinal causes: malnutrition, anorexia, maldigestion, malabsorption
- Special forms of renal osteopathies

3. Neoplastic diseases:
- Multiple myeloma
- Diffuse filiarisation

4. Inflammatory diseases:
- Rheumatoid arthritis
- Crohn's disease, colitis ulcerosa

5. Hereditary bone disease:
- Osteogenesis imperfecta
- Hypophosphatasia

6. Immobilisation:
- Paraplegia
- Space flight

Based on the pathogenesis of osteoporosis, it is common to characterize the medicaments for osteoporosis according to their mode of action (table 2) [2, 3]. Bone loss in osteoporosis depends on increased resorption as well decreased formation.

Antiresorptives are drugs which *inhibit exaggerated osteoclast activity*. In the first line, we find the **estrogens**: estrogen-deficiency is followed by increased bone resorption (see below); estrogen replacement normalizes the situation – increased resorption and turnover is calmed down to normal.

30 years ago, the discovery and investigation of **calcitonin** showed that it inhibits overactive osteoclasts. Over one decade calcitonin had the privilege to be the first and only drug for all diseases presenting with increased bone resorption. Then the development of the **bisphosphonates** yielded a still more potent anti-osteoclastic principle. Nowadays the bisphosphonates have replaced the calcitonins because of their higher potency and more stable efficiency in most indications.

The search for further antiresorptive drugs is going on – e.g. flavonoids, echistatin, CSE-inhibitors are under investigation. For practical medicine, they do not yet play a role.

Anti-estrogens like tamoxifene have been further developed to the family of "selective estrogen receptor modulators" (**SERM**). Ideally SERMS are antiresorptives at the skeletal-tissue, but neutral at the estrogen-depending female organs like breast and uterus. Favourable effects also are expected for the lipid metabolism. SERMS are important alternatives within the differential treatment of osteoporosis.

Theoretically, *stimulators of osteoblast activity* would be ideal drugs for osteoporosis. Here, the spectrum of drugs is smaller. Still **fluorides** are drugs of first choice, but they require knowledge and experience. They were criticized because of uncritical dosing (see below) which included under- as well as over-dosages. For the metabolic skeletal condition of low turnover they are still to be preferred.

Anabolics also exert a certain formation stimulating effect. Because of the misuse by sportsmen and -women they were not anymore exactly studied for medical purposes. Therefore, data from studies are rare. We think that anabolics are helpful in some special cases (see below).

Already over many years the field discusses whether it is possible to stimulate bone formation via an *activation of bone turnover*. The treatment using **parathormone** (PTH) yielded interesting results in animal experiments

Table 2. Principles of drug treatment of osteoporosis

Inhibitors of bone resorption ("antiresorptives")	Stimulators of bone formation ("anabolics")
In case of high turnover due to estrogen deficiency: • estrogens (plus progestagens, if not hysterectomized) • classical antiestrogens (tamoxifene) • selective estrogen receptor modulators (SERM) • modified estrogens type tibolone • calcitonins • bisphosphonates (alendronate, etidronate, pamidronate, risedronate) In case of high turnover due to calcium- and vitamin D-deficiency → secondary hyperparathyroidism: • calcium plus • vitamin D	In case of low turnover: • fluorides (NaF, MFP) • anabolic steroids (nandrolone, stanozol) • PTH • (? – growth hormone)

as well as in smaller studies in men. Recent studies showing increases in bone mineral density and decreases in vertebral fractures are promising.

During the last years also **growth hormone** was used with a similar intention. The results are still incomplete – we do not recommend growth hormone treatment in osteoporosis outside controlled studies.

A factor of special importance for calcium-metabolism and bones is **vitamin D** and 1.25-dihydroxy-vitamin D, it's active metabolite, the so called vitamin D-hormone (calcitriol). Physiological low doses activate the osteoblasts, especially when they are devoid of vitamin D. Excessive doses may even stimulate bone resorption. But if increased resorption was induced by vitamin D deficiency including the induction of secondary hyperparathyroidism, adequate doses of vitamin D indirectly exert anti-resorptive effects. Substitutive doses of vitamin D are components of the so-called basic treatment of osteoporosis including also calcium.

If a physician is looking for informations regarding the medicinal treatment of osteoporosis, the field is influenced by different intentions. Independent experts try to give a neutral view (see the present monography) including unanswered questions and economic considerations. Informations from manufacturers do not promise to cover the whole field. Recommendations of one drug often do not comment the limits of it's efficiency – the reader will not find recommendations for competitor companies' drugs although they might be more useful in the single case. Very cheap and not patented drugs are not examined in studies any more, therefore the pattern of economic and promising treatment has to be put together like a mosaic.

The physician should forget the expectation that there is one "broadband" anti-osteoporotic drug which could be used for all types and forms of osteoporosis with identical efficacy. The medical world is waiting for more comparative treatment studies in order to compare the potency of drugs with different mechanism of action. Such data are rare – the prescribing doctor has to fill in the blanks which are found even in the studies of EBM-standard.

Figure 1 explains why all therapeutic principles enlisted in table 2 may be useful – however the mechanism of action favours their use at different steps of bone loss [4]. After the decrease in blood estradiol at the time of menopause, bone turnover is accelerated. During this phase resorption surpasses the compensatory new bone formation. This results in a negative bone balance. Estrogen-loss leads to an increase of cytokines which stimulates bone resorption (e.g. interleukin 1, interleukin 6). There is no definite proof that a fall in blood calcitonin which was formerly discussed as a contributing cause is really of importance. Three different, but equally acting therapeutic principles to inhibit the increased osteolysis are at disposal: estrogens as well as their variants, the SERMS, calcitonins, bisphosphonates.

Due to the increased resorption of skeletal tissue calcium is released into the circulation. However, this does not produce hypercalcaemia. The slight increase in blood calcium increases renal calcium excretion as well as a fall in PTH. Lower PTH-levels contribute to increased calciuria because the PTH-effect which increases calcium-reabsorption in the kidneys is diminished. Even healthy women excrete after the loss of estrogens about 30 mg/day more than premenopausally. Women with fast loss may excrete the double or tri-

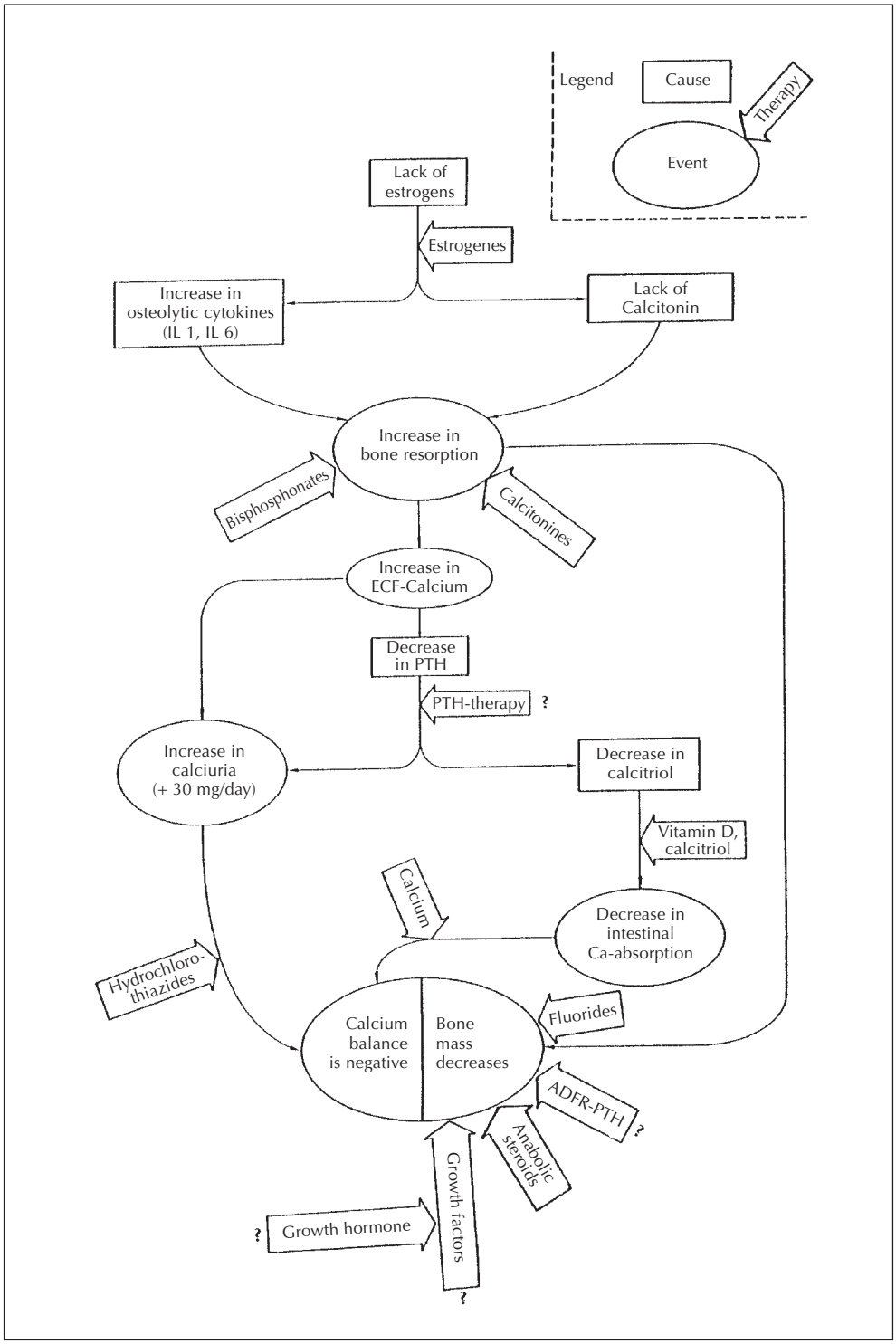

Figure 1. Pathogenesis of osteoporosis. The arrows indicate where respective drugs are active.

ple of these 30 mg in addition to their normal calcium loss. 30 mg calcium per day signify the loss of 1% of total bone calcium per year, e.g. 10 g taken out of 1 kg. Thus, high turnover due to lack of estrogens is accompanied by **lowered** PTH. Low PTH is not only accompanied by increased calciuria, but also by decreased formation of calcitriol. This relative lack of calcitriol leads to a decreased intestinal calcium absorption even if calcium supply is unchanged. Negative calcium balance stems from 2 components: Increased renal loss, decreased intestinal absorption. To compensate for these losses calcium can be supplied in larger doses than premenopausally, vitamin D can be optimized. Calciuria may be minimized by administering hydrochlorothiazide e.g. in case of kidney stone disease.

In case these events were not therapeutically influenced, after a certain time of negative balance a respective amount of bone has been lost. Now it is recommended to stimulate bone formation as the speed of increased resorption calmed down after about one decade. Stimulators of new bone formation are fluorides, in special cases anabolics may be used. PTH may be the stimulator of the future. Studies using growth hormone are on the way.

By no means formation stimulators can be replaced by anti-resorptives or vice versa. But this biological evidence is not very transparent from studies omitting this differentiation.

Prerequisites for differential treatment: Assessment of bone turnover speed

From figure 1 it is evident that osteoporosis drugs can not be exchanged as

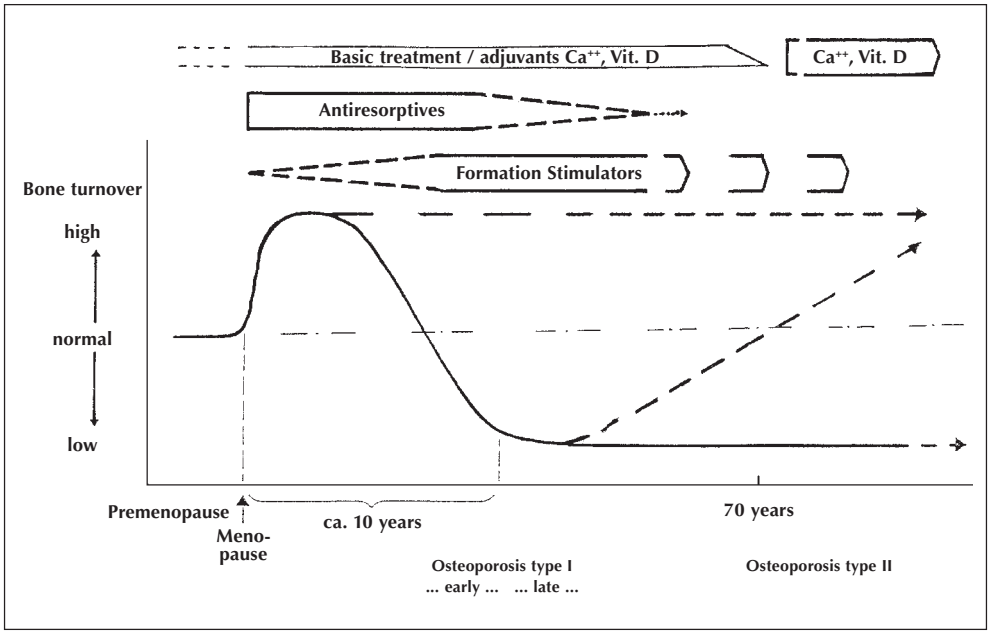

Figure 2. The course of bone turnover after the menopause as an indicator for the choice of treatment.

one likes. Anti-resorptives have another mechanism of action than bone formation stimulating agents – how to use them?

This is illustrated in figure 2 depending on the speed of bone turnover. Before the menopause as long as estrogens are still present, women exhibit the normal mean speed of bone turnover of adults, as it is also shown by eugonadal men. After the menopause, bone resorption is accelerated as described. The phase of bone high-turnover lasts for about 8–10 years. It is not only logical but also proven by differentiating studies that anti-resorptives are very efficient during this condition.

After about one decade bone turnover slows down, obviously bone tissue is not any longer depending on estrogens. Of course, low turnover can be masked if other resorption stimulating factors like hyperparathyroidism are present. This has to be excluded.

At low bone turnover drugs which stimulate bone formation are to be preferred. Anti-resorptives are not fully inactive – however, their effect could be so small that bone mass and density are not adequately improved. Treatment of choice is an osteoanabolic principle, e. g. fluorides, in special cases anabolics, perhaps in the future PTH. The low turnover phase of the skeleton starts about 10 years after the menopause and lasts up to the senium as long as other osteoporotic noxes do not induce another type of high turnover.

At the age of 80, only few and "healthy" living women are optimally nourished with calcium and vitamin D and physically active enough to get enough sun for endogenous vitamin D formation. The majority of this population exhibits another type of high turnover: Insufficient calcium supply and hypovitaminosis D in combination with decreased mobility and physical exercise (life in old-people's homes) induce secondary hyperparathyroidism. There is a clear difference between postmenopausal high turnover accompanied by low PTH and senile high turnover accompanied by secondary hyperparathyroidism. Of course, anti-resorptives will also inhibit osteoclasts under this condition, however, causal treatment is to be preferred. Studies have shown that simple calcium and vitamin D are efficient in reducing osteoporotic fractures, especially hip-fractures which are typical for osteoporosis type 2 (in contrast to osteoporosis type 1 which primarily affects cancellous bones like the vertebra).

How to diagnose the speed of bone turnover? In the majority of cases, taking the history carefully and performing the physical examination with experience is sufficient. If the first vertebral fracture occurs in a woman a mere five years after menopause, it is presumable that her skeleton is in a high turnover condition. If the first fracture happens 15 years after the menopause, low turnover can be assumed (of course, all risk-factors like lack of calcium and vitamin D have to be excluded). If a woman of 80 years suffers a hip-fracture, her appearance and life conditions will help to differentiate between high and low turnover: The typical high turnover case will be pale, reduced in mobility and not optimally supplied with calcium. In contrast, the still active old lady seeing the sun even in wintertime and eating sufficient nutrients containing calcium will be rare.

Experienced physicians may try to get additional informations from bone turnover markers. However, there is a broad overlap between healthy bone and osteoporotics. Fresh fractures of course influence the markers and may turn a low turnover case due to an active callus into a high turnover.

Measuring several markers does not help at all – it is recommended to gain experience using e. g. bone specific alkaline phosphatase for bone formation and pyridinium crosslinks in urine for bone resorption. Additional parameters like PTH and 25-OH-vitamin D are to be considered if history and clinics are uncertain. Forms of secondary osteoporosis have to be excluded [5, 6]. If the bone turnover situation is still unclear, bone histology from a transiliac biopsy may be helpful. Bone histology of course yields the most reliable diagnosis of bone turnover.

Antiresorptive treatment

Immediately after the menopause, the most physiological treatment of osteoporosis is **hormone replacement therapy** (HRT). The substitution with estrogens slows the acceleration of bone turnover; several percents of bone density may be regained. Many prevention studies have documented the efficacy, but also manifest osteoporosis presenting with fractures is improved [7]. Recommended doses are those which prevent bone loss in prevention studies (see chapter on HRT). It goes without saying that women who are not hysterectomized require in addition progestogens. The duration of treatment depends on the risk situation. Normally 8–10 years are recommended (regular gynaecological controls are mandatory), high risk situations may require longer times. If estrogens are started after the phase of high turnover, identical doses of estrogens lead to smaller effects [8]. Now formation-stimulating agents are to be preferred or at least recommended in addition to HRT (see next paragraph).

If the patient does not want to use HRT or if there is a family history of breast cancer, estrogens may be hazardous. Then the use of anti-estrogens like tamoxifene may be useful [9]. Tamoxifene revealed to be anti-estrogenic only at the breast whereas an intrinsic estrogen effect persists at the skeleton.

Still better for the situation of osteoporosis is the use of a **selective estrogen receptor modulator (SERM)**. Typical representatives like raloxifene have no estrogenic effect at breast and uterus – hopefully they exert even a certain protective effect against breast cancer. The osteoprotective effect persists as well as possible positive effects on lipid metabolism [10]. Osteoprotection is documented for the spine, where bone density is increased and the number of fractures declines [10]. It can not be excluded that the osteotropic potency of raloxifene is somewhat smaller than that of natural estrogens plus progestagens.

Another variant in this section is **tibolone**. It exerts a partial estrogen activity besides a partial androgenic progestagen activity with documented osteoprotection [11]. During the next years it has to be worked out how breast cancer risk, osteoporosis risk and also cardiovascular risk permit differential recommendations for the use of the estrogen variants. To date comparative studies in particular are lacking.

If women with overt high turnover osteoporosis reject estrogens, calcitonins or bisphosphonates may be administered alternatively. Studies using **calcitonin** have documented the prevention of postmenopausal bone loss. Data for overt osteoporosis are scarce [12, 13]. Nevertheless it can be assumed that calcitonin treatment may be useful for high turnover osteoporosis. Recommendation for dosing range from 100 units daily or 3 times 50 units per week

s.c. It is irritating that a recent study (PROOF) reported a reduction in vertebral fractures for a medium dose of calcitonin, whereas lower as well as higher doses were found to be not effective [14]. Those results produce some uncertainty with respect to the optimal dose for each individual patient. Calcitonin injections may induce side effects like nausea and vomiting. Sometimes the administration of salmon calcitonin induces neutralising antibodies making the hormone ineffective. It has been shown that calcitonin was less effective at low bone turnover compared with high turnover [15].

Bisphosphonates are the most potent inhibitors of bone resorption. Several representatives were tested and introduced. To be recommended are etidronate, alendronate, risedronate. Etidronate is taken orally at a daily dose of 400 mg during 2 weeks, the remaining 76 days of a cycle of 3 month containing calcium supplementation. The duration of treatment is 2–3 years or longer. Studies documented the increase in bone mineral density and the decrease in osteoporotic fractures [16].

The daily dose of alendronate is 10 mg continuously. The drug has to be taken fasting in the morning with some water, afterwards the patient has to stay

Table 3. Treatment of osteoporosis using antiresorptives

Drug group	Doses	Duration	Remarks
Estrogens (combined with progestagens) [7, 8]	See chapter HRT: eg, 0.6 mg conjugated estrogens or 1–2 mg estradiol	8–10 years	Gynecological controls mandatory
Antiestrogens (eg, tamoxifene) [9]	20–30 mg per day	1–2 years (longer?)	In case of breast cancer risk
Selective estrogen receptor modulators (**SERM**), raloxifene [10]	60 mg per day	2–4 years (longer?)	In case of breast cancer risk
Modified steroids: **tibolone** [11]	2.5 mg per day	1–2 years (longer?)	Alleviates climacteric complaints – extent of osteoprotection?
Calcitonins (salmon, human) [12–15]	Between 100 IE per day and 3 x 50 IU per week (subcutaneous; nasal)	1.5–2 years	Side effects: nausea, vomiting. Neutralizing antibodies were seen (SCT).
Bisphosphonates: Etidronate [16]	400 mg per day during 14 days, then 76 days calcium	2–4 years and longer	
Alendronate [17, 18]	10 mg per day fasting in the morning, separately calcium	2–4 years and longer	Cave: oesophagitis
Risedronate [19]	5 mg per day fasting in the morning, separately calcium	2–4 years and longer	
Pamidronate [20]	30 mg intravenously (over several hours) every 3 month	2–4 years (and longer?)	Febrile reaction without relevance

upright for at least 30 minutes in order to avoid oesophageal irritations. Calcium is taken later during the day, separate from the bisphosphonate. Duration of treatment is 2–3 years, perhaps longer. Studies documented the reduction in vertebral fractures, but also peripheral fractures like hip-fractures (although the latter ones were rather rare) [17]. In comparative study using alendronate and calcitonin, the bisphophonate showed to be much more potent as an antiresorptive [18].

Risedronate is taken in a dose of 5 mg/day continuously – the results are comparable to the other bisphosphonates [19]. Intravenous bisphosphonate treatment is very useful in patients with an irritable gastrointestinal tract or the need to take many other oral drugs. 30 mg of pamidronate i.v. every 3 months induce the typical increase in BMD [20].

It is a great disadvantage for most studies using bisphosphonate that there is no differentiation between high turnover and low turnover, neither during the stratification for the study nor during the evaluation. Nevertheless there are similar hints as for the estrogens and the calcitonins that the effect of bisphosphonates is more pronounced in high bone turnover, as to be expected [21]. Therefore we think that bisphosphonates are drugs of first choice in cases of high turnover osteoporosis, but not in cases of low turnover.

Table 4. Treatment of osteoporosis using formation-stimulating agents

Drug group	Doses				Duration	Remarks
	Full dose F^-	½ dose F^-	Adjuvants			
			Calcium	Vitamin D		
Fluorides NaF sodium fluoride [22–24]						
Ospur F 25 mg NaF Baer 25 mg Ossiplex ret. 25 mg	3 Tbl. = 33.9 mg	2 Tbl. = 22.6 mg (rarely 1 tbl. = 11.3 mg)	1.000 mg	1.000 IU	3–4 years	Annually BMD: if 8–10% per year, dose reduction
Ossin 40 mg	2 Tbl. = 36.2 mg	1 Tbl. = 18.1 mg				Annually x-rays
Monofluoro- phosphate, MFP [24, 25] Tridin	4 Tbl. = 20 mg	2 Tbl. = 10 mg	(Contains 150 mg Ca per tablet)	1.000 IU		In case of lower limb pain syndrome, dose reduction
Monotridin	2 Tbl. = 20 mg	1 Tbl. = 10 mg	1.000 mg	1.000 IU		
Anabolics Nandrolone- decanoate [26]	25–50 mg i.m. every 3–4 weeks				1–2 years	Cave: virilizing side effects

Formation-stimulating treatment

Treatment of choice is still the use of **fluorides**, if low turnover osteoporosis is diagnosed. Stimulation of osteoblasts is necessary, because the inhibition of the few active osteoclasts will not yield sufficient gain in bone mass. Fluorides increase the effect of endogenous growth factors on osteoblasts. Studies from the USA threw doubts on the efficacy of fluorides – the explanation is the use of unnecessarily high doses of fluorides without individual adaptations. Such high doses may induce osteosclerosis and increased bone fragility [22, 23]. Fluorides can not be administered in a uniform dose over years without adaptation. The therapeutist has to know the therapeutic window and he has to observe the patient's response. The therapeutic window has the following limits: Too low doses are inefficient, too high doses induce osteosclerosis and the loss of bone stability.

The following procedure is recommended (table 4). We start with a full dose in order to avoid undertreatment. If too low doses for the individual patient are given in the beginning, years may be lost until underdosing is recognized.

How to monitor treatment? Using the full dose, 20–30% of patients develop a lower limb pain syndrome, typical for fluoride treatment, during the first months. Pains and swellings around the ankles may mimic a rheumatic disease. The symptoms are caused by microfractures, appearing on the x-rays as intense zones in the calcaneus or distal tibia. Bone scintigraphy shows hot spots in this regions. Instability or real fractures never happen. If such symptoms do appear we recommend to suspend fluoride treatment for 4 weeks, and to later continue treatment with half of the dose (table 4) [24]. Fluoride treatment requires yearly osteodensitometry. If there is an increase in bone density higher than 8–10%, the risk of osteosclerosis can not be excluded. A dose-reduction is recommended.

Following these recommendations, consequent fluoride treatment for 3–4 years may increase bone mass and density by 15–20%; further bone increase beyond this range is not desirable. Adjuvants are calcium (1,000 mg/day) and vitamin D (1,000 units/day). If the fluoride drug is sodium fluoride, calcium should be administered separately (we prefer to give sodium fluoride after dinner, in this case calcium in the morning or at noon time). If monofluorophosphate (MFP) [25] is taken as the source of fluoride, the separation from calcium is not necessary. Fluoride from MFP is absorbed by more than 90%, therefore the recommended daily dose (20 mg F^-) is identical with the drug content. From enteric coated sodium fluoride preparations, only about 60% of fluoride is absorbed – this explains the higher dosing (table 4).

In case of high turnover osteoporosis we do not recommend fluorides as single treatment. At least in the beginning, antiresorptives should be given until a low turnover situation is achieved. Combination therapy could be useful, but is not yet proven to be more potent than the treatment with the single principles.

Anabolics were used for the treatment of osteoporosis 30 years ago, but their use was aborted due to side effects caused by overdosing. During the last years studies using more cautious dosing showed that anabolics may increase bone density in osteoporosis. On the one side they exert substitutio-

nal effects in the situation of postmenopausal sex hormone deficiency, on the other side they are superior to estrogen effects due to their musculotropic effects (which led to the misuse in sports and bodybuilding). Compared to estrogen treatment, the addition of anabolics yielded a better effect [26]. A treatment option for example is nandrolone decanoate, 25–50 mg every 3–4 weeks i.m. Treatment experience is available for 1–2 years, there are no data for longer duration. Side effects like virilization have to be watched. Hyperlipidemic patients should be treated with great caution. Generally it is recommended, to administer anabolics not yet during the first decade after the menopause, but perhaps after the age of 65 or 70.

Empirical efforts to stimulate bone metabolism especially in the low turnover situation follow the ADFR-Scheme: First step is the activation (A) of bone turnover by giving PTH, thyroid hormone or others. During phase 2 the activity of the osteoclasts is depressed (D) in order to avoid large defects. Then during phase 3 the osteoblasts which are activated by the osteoclasts should form new bone in a free interval (F = formation or free interval). Finally, after the cells fall back to low activity, the cycle has to be repeated (R = repetition). PTH plays the main role at the moment, perhaps combined with estrogens [27]. Recent studies using PTH alone revealed an increase in bone density as well as a decline in vertebral fractures [28].

Another hormone which is discussed for the treatment of osteoporosis is growth hormone [29]. Patients suffering from pituitary insufficiency exhibit lower bone density especially due to lack of growth hormone. They seem to profit from a growth hormone substitution. If the same hormone is useful in patients without growth hormone deficiency, is unclear and under investigation. Scientists are also looking for the effects of growth factors (somatomedins).

Basic treatment: Calcium and Vitamin D

The extent to which a lack of calcium and vitamin D contributes to idiopathic osteoporosis is not always evident and presumably differs from country to country. In Japanese women, osteoporosis seems to be combined with a very low calcium intake, and the response to calcium and vitamin D is rather good [30]. Middle-Europe, including Germany, may exhibit a more pronounced lack in vitamin D compared with the USA – their southern parts (California, Florida) have a more intense sun exposure and milk is fortified with some vitamin D. For Germany the recommendation is justified that all adults should have a calcium intake of 1,000 mg/day. During summertime, 20–30 minutes per day of sun exposure will suffice, however, the low sun intensity in winter will not guarantee a sufficient vitamin D production in the skin.

After menopause, the optimum calcium intake for women without HRT rises to 1,500 mg. The same amount is recommended for both sexes after the age of 65. Especially slim women who avoid any weight gain do not take in the recommended amount of calcium (milk and dairy products also contain a lot of calories). Then mineral waters rich in calcium are a useful alternative. As a rule, separate calcium preparations are not needed as long as the calcium content of food and fluids has been calculated and reaches the optimum.

In case of *overt osteoporosis* with fractures any risk of insufficient calcium supply should be avoided. Every drug treatment requires accompanying basic treatment, this is especially true for substances which simulate bone formation (fluorides). Calcium preparations now are useful, if nutritional optimal calcium supply can not be guaranteed. Basic calcium treatment amounts to 500–1,000 mg calcium per day as well as 500–1,000 units vitamin D per day. In case of postmenopausal high turnover, calcium and vitamin D accompany antiresorptives, in case of low turnover they accompany fluorides (or anabolics). Basic treatment with calcium and vitamin D is of great importance in case of osteoporosis type 2 with a high turnover due to secondary hyperparathyroidism (see above). Studies in France and USA documented the efficacy of such prophylaxis [31, 32]. The transfer of these experiences to overt osteoporosis type 2 is justified. Whether it is useful to add other drugs, has to be decided after each individual case analysis.

Patients with hip fracture and nevertheless low bone turnover (without calcium deficiency) may need anabolic treatment, in case of a sufficient long life expectancy also fluorides may be justified. Indirect calcium therapy by diminishing calciuria using hydrochlorothiazides may be useful in individual situations: If an osteoporotic patient suffers from hypertension, furosemide as a diuretic drug is not a good choice because it increases calciuria. In contrast, a hydrochlorothiazide does not only decrease calciuria (turning calcium balance to a positive level), but it also lowers blood pressure. Another situation is recurrent kidney stone disease: In a patient suffering from osteoporosis at the same time, treatment with calcium is not recommended. Using a hydrochlorothiazide aids kidney stone prophylaxis by decreasing calciuria, while at the same time the non-excreted calcium is at disposal for the bone tissue.

Some studies e.g. from Japan [30] have demonstrated that vitamin D metabolites could be more efficient than simple calcium treatment. It is a pity that such studies always only test a vitamin D metabolite without testing in a control arm simple (and cheap) genuine vitamin D [33]. But the already mentioned studies from France and USA have shown that aged people including those around 80 being adequately substituted with simple vitamin D and calcium show a definite reduction of fractures [31, 32]. Until a study using vitamin D and a metabolite in equipotent dosages proves the superiority of the metabolite, there is no reason to prefer a more expensive metabolite to genuine vitamin D.

Secondary osteoporosis

In case of secondary osteoporosis it is necessary to treat the causing disease and osteoporosis (which is in some cases identical). The most common type of secondary osteoporosis is glucocorticoid-induced osteoporosis (GIO). In case of long-term glucocorticoid therapy (6 month and longer) with doses of more than 7.5 mg prednisolone aequivalents it is recommended to perform "minimal prophylaxis" with 1,000 mg calcium and 1,000 units vitamin D per day to counteract glucocorticoid-induced impairment of calcium absorption.

If in spite of this prevention the loss of bone density continues (BMD measurements are recommended every 6–12 months), fluoride treatment is to be discussed (dosages see table 4). Fluorides also proved to be effective in GIO

after heart and liver transplantation [34].

In case of higher dosages of glucocorticoids as well as pre-existing osteoporosis, bisphosphonates can be administered from the onset of glucocorticoid treatment. Data for the effectiveness of etidronate and alendronate have been presented [35, 36]. Whether bisphosponates are also helpful in established GIO after the initial phase of fast loss (one year) has passed, is unanswered. Late GIO presents a low turnover which is the reason for our recommendation to use fluorides [37].

If secondary osteoporosis is caused by multiple myeloma or other diffuse neoplasias, the individual therapy should include bisphosphonates. They have also proved to be useful in humoral hypercalcaemia of malignancy (HHM) as well as in bone metastases due to breast or lung cancer and others. Secondary osteoporosis due to hyperparathyroidism or hyperthyroidism shows reasonable recovery after healing the endocrinopathy. Additional efforts to improve bone mass and density are seldomly required.

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