Prophylaxis of Osteoporosis with Estrogens

M. H. BIRKHÄUSER

Introduction

In the early forties, Albright [1] clearly identified the connection between estrogens and bone mineral content, and showed that bone metabolism is estrogen-dependent. However, it took another 30 years for this pathophysiological concept to prevail in clinical practice. Today it is generally accepted that any form of ovarian insufficiency with an estrogen deficiency exceeding six months results in a metabolic shift in bone metabolism that increases bone turnover. The destruction of bone mass predominates over bone formation, which leads to a massive increase in the risk of a clinically relevant loss of bone density, and subsequently to an increase in fracture risk.

The principle of hormonal prophylaxis for osteoporosis was introduced some thirty years ago. Initially, only estrogens were administered, which is only permissible in women with hysterectomy. Today, hormone replacement with a combination of estrogen and progestagen is routine in women with an intact uterus in Europe. As a principle, not only older women with an increased risk of osteoporosis, but also every younger woman with amenorrhea of more than six months duration should receive estrogen replacement. The omission of replacement therapy in a premenopausal woman with amenorrhea is now regarded as a mistake, since the later postmenopausal fracture risk depends largely on the bone mass present at the time of the menopause.

Osteoporosis Risk and Estrogen Effects in the Bone: Common Considerations

Peak bone mass is determined individually, on the one hand by genetic factors, and on the other hand by the production of sexual steroids during the important years of adolescence and by lifestyle [2, 3]. Africans, for example, have a higher bone mass on average than Europeans or Asians. Since a woman's peak bone mass is acquired in adolescence, especially between the age of 11 and 18 years, and since the possibility of a further, limited increase in bone mass ends with the age of 30 at the latest, a normal endocrine milieu and thus normal estrogen production with regular cycles in adolescence is just as important as a healthy diet and sensible life-style [4–6]. Once the peak bone mass has been reached, the annual bone loss rate until the menopause is approx. 0.7 %, then it rises to 5 % in the trabecular bone and to 1–1.5 % in the whole skeleton for several years, and finally it normally drops to the age-related loss rate again. After the menopause, bone loss is highest in fair-skinned European or Asian, thin and

physically inactive women, and lowest in African women [7, 8]. In heavy smokers, the risk of a femoral neck fracture is increased by 40–45 % [9]. The decisive factors are sufficient calcium intake (in the postmenopause 1500 mg/day without HRT and 1000–1200 mg/day with HRT), and sufficient intake and activation of vitamin D [10]. Regular exercise improves bone density [11–14]. The unfavourable effect of treatment with glucocorticoids can be diminished by hormone replacement therapy (HRT) [15, 16].

Contrary to common assumption, there is no correlation between the severity of subjective climacteric symptoms and the decrease of bone mass in the spine and femoral neck [17, 18]. However, there is a certain correlation between the baseline values for bone density on the one hand and age at the time of menarche on the other hand. This correlation is significant for the femoral neck. Late menarche usually implies reduced bone density. A high body mass index results in better bone mass, partly via increased acyclical, peripheral aromatized estrogens, partly via mechanical factors (greater burden on the bone!) [19]. However, it is incorrect to assume that obese women in general do not have an increased osteoporosis risk after the menopause.

Estrogens reduce primarily the accelerated bone absorption and only secondly the bone destruction. This results in a transient positive bone balance. Thus, the bone density increases in the first phase of estrogen administration, but the effect flattens with ongoing HRT. Estrogens presumably modulate the bone metabolism by inhibiting the osteoclast activity through various local autocrine and paracrine factors [20]. Estrogen deficiency leads to the predominance of osteoclast activity with increased bone destruction.

Estrogens probably improve calcium absorption via 1,25-dihydroxy-vitamin D [21]. This process is not age-related. The protective effect of estrogen on the bone is proportional to the serum level of endogen estrone and estradiol production [22] respectively to the administered estrogen dose [23–25]. Unfortunately, it is still not known well enough that estrogen deficiency in young women with primary or secondary amenorrhea can cause severe loss of bone substance even after a fairly short duration [26].

INFLUENCE OF ESTROGEN ADMINISTRATION ON FRACTURE RATE

In addition to the numerous investigations of osteoporosis prevention with estrogens and progestagens, in which surrogate parameters such as bone density or biochemical bone parameters were measured, there are also studies on the fracture rate during HRT, showing that HRT offers significant protection against osteoporotic bone fractures [27, 28]. However, this requires that the treatment should be continued for several years. The minimum duration of treatment appears to be five years, according to other opinions it is closer to ten years. An insufficient duration of HRT administration or merely local administration of estrogens, e. g. for the treatment of subjective symptoms during the first years after the menopause, do not guarantee long-term protection against osteoporotic fractures. Cohort studies have shown that long-term HRT reduces the incidence of spinal deformations in the postmenopause by about 90 % [29]. Other data show that HRT reduces the risk of radius and

femoral neck fractures by about half over a period of at least six years.

In order to obtain optimal compliance, the form of administration of the hormonal osteoporosis prophylaxis must be determined individually according to the needs and preferences of each woman. It is essential to achieve optimal acceptance if we want to provide long-term prophylaxis over several years. The basic principles of each hormone replacement therapy are shown in Table 1. Contrary to the still common practice in the United Stated, the administration of estrogen alone without gestagen in women with an intact uterus is contraindicated in Europe.

Table 1. Hormone replacement with estrogens and gestagens after the menopause: Basic principles

1. Choice of estrogen:
- Conjugated ("natural") equine estrogens
- 17-beta estradiol

Alternatives:
- Tibolone
- SERMs
- Oral hormonal contraceptives: only in the perimenopause, only for non-smokers without cardiovascular risk factors

2. Choice of galenic form:
- Oral
- Transdermal (percutaneous)
- Intramuscular
- Intranasal
- (Vaginal, e.g. vaginal ring)
- (Implants)

3. Progestagens:
Co-administration of a progestagen with a classical estrogen is imperative, in order to
- avoid the increased risk of endometrial carcinoma with estrogen monotherapy,
- support the bone-protective effect of estrogen, depending on the progestagen (does not apply to all gestagens, see text).

4. Individual adjustment of the therapy regime

INFLUENCE OF THE PROGESTAGEN COMPONENT

The extent to which the progestagen component is actively involved in osteoporosis prevention has only been partly explored [30]. Progestagens definitely do not counteract the osteoprotective effects of estrogen [30]. In fact, it would seem that some progestagens, such as norethisterone acetate (NETA) and gestronol hexanoate, actually have their own osteoprotective activity [30–32], whilst medroxyprogesterone acetate (MPA) alone does not have any osteoprotective effect. The osteoprotective action of NETA has also been confirmed in postmenopausal women who received NETA as an add-back therapy during GnRH treatment for endometriosis [33]. In the GnRH monotherapy group, bone loss occurred after 6 months and was prevented by co-administration of NETA.

PREVENTION IN THE FERTILE PHASE, THE PERIMENOPAUSE, AND THE EARLY POSTMENOPAUSE

Regardless of the cause and the age of the patient, any hypothalamic estrogen deficiency can lead to clinically relevant disorders of bone and lipid metabolism. Whilst normal physical activity and healthy diet can improve bone mineral content in pre- and postmenopausal women, estrogen deficiency in top athletes with secondary amenorrhea and in rare cases primary amenorrhea in young girls due to a shift in menarche can lead to an inadequate formation of the peak bone mass and

thus to a markedly reduced bone density [34]. The same applies to women with anorexia nervosa or bulimia, and to those with hypothalamic amenorrhea with other causes.

The loss of bone mineral content correlates with the duration of amenorrhea and the body weight, regardless of the cause. Even in young women with amenorrhea aged between 18 and 25 years, bone densities as in women aged 50–70 years can be found [26].

Although designer estrogens may also offer protection against osteoporosis, as is achieved with the classic oral hormonal contraceptives in the perimenopause, natural estrogens should be used whenever contraception is not an issue. Every young woman with amenorrhea must receive hormone replacement with an estrogen-progestagen combination. If contraception is also required, a modern low-dose birth-control pill can be selected instead of the usual substitution. In adolescence, the protective effect must however be monitored [35].

Once the peak bone mass has been reached, the bone density remains virtually unchanged until the onset of menopause. With normal nutrition, the calcium balance is usually good and there is no loss of bone mass [36]. With the progressive deterioration of ovarian function in the perimenopause, the bone destruction starts to predominate over bone formation: After the menopause, the bone destruction rate rises faster than the formation rate and the calcium balance is negative. The aim of every osteoporosis prevention is to return the bone metabolism to its premenopausal levels, and if possible the bone formation rate should surpass the destruction rate again.

With progressive postmenopause, the bone density decreases [37, 38] and the fracture incidence increases [39]. The critical threshold for bone fractures after inadequate trauma is first reached in the spine. A few years later the increased incidence of femoral neck fractures follows [40–42]. Like natural, timely menopause, premenopausal bilateral castration leads to a decrease in bone mass that follows precisely the same pathophysiological rules and has the same clinical consequences with regard to osteoporosis risk as the estrogen deficiency after natural menopause. Less well known is the fact that bilateral castration in the first years after the menopause will accelerate the bone loss, since the residual steroid secretion by the ovaries, especially of ovarian androgens, is eliminated as a result [43]. The ovary is not the inactive and useless organ that it is sometimes thought to be after the menopause; instead, it continues to have a major endocrine physiological function [43–45].

Bone loss of 0.5 to 1 % per year may still be regarded as physiological and as a consequence of ageing [46–48], but a loss of 3 % or more per year is definitely pathological: This is a clear indication for hormone replacement [30]. The most reliable and now most commonly used method to determine bone density is dual-energy x-ray densitometry or DEXA [49, 50]. With the DEXA method, bone density can be measured in the spine, the femoral neck and the tibia, and its precision is approx. 1 %. Measurements using peripheral quantitative computerized tomography (pQCT), on radius or tibia, are extremely precise, but they do not allow an assessment of the spine. Ultrasound bone density measurements provide a good screening, but they are not representative for other bone regions than the actual scan site. However, studies investigating the correlation

between the peripheral measurement sites of the various sonographic methods and the vertebral bone or femoral neck should be available soon.

Like the classical administration of combined estrogen and progestagen, pure estrogen replacement therapy in women after hysterectomy provides osteoporosis prevention in postmenopausal women [51–53]. This beneficial effect is independent of both the chronological and the menopausal age. Osteoporosis prophylaxis with estrogens decelerates bone loss in all regions of the skeleton, both in trabecular and in cortical bone [51, 54–56]. It does not matter whether peroral or transdermal (gel, patch) administration is chosen for osteoporosis prevention: Both offer an efficient protection [31, 57]. At our clinic, we compared the protection of bone mass in spine and femoral neck of two of the most common administration forms, transdermal and peroral estrogen, whereby both groups received cyclical dydrogesterone. A third group served as a control. Both peroral (2 mg estradiol) and transdermal estrogen (50 μg estradiol) led to a significant increase in bone density within 12 and 24 months. At the same time, there was a significant loss of bone mass in the untreated control group [58]. These observations correspond with those of various authors who used other progestagens [59] or other forms of administration [51, 57, 58, 60, 61].

Even if there are no age limits for the induction of hormone replacement, it should be started as early as possible after the menopause for full benefit, since the greatest bone loss occurs in the first 3–5 years after the menopause. Minimum duration of replacement therapy to guarantee osteoporosis prophylaxis is estimated at 5–10 years (see below). The fracture risk decreases in proportion to the duration of hormone replacement. If we take the mean life expectation today into account, osteoporosis prophylaxis should be continued up to an age of about 75.

It is still advisable to use the classical estrogen dosages (Table 2) in the perimenopause and early postmenopause [50, 62, 63], since it is during this period of life that the treatment of subjective complaints such as hot flushes, mood changes and sleep disorders is the central issue. However, more recent studies have shown that even lower dosages may be sufficient [45, 52, 64–66].

Even if osteoporosis prevention is the only indication, the generally known principles that apply to hormone replacement therapy (HRT) after the menopause should be respected. The risk-benefit ratio must be discussed in detail with every woman.

Prevention in the Later Postmenopause

With increasing time since the menopause, there is usually a deceleration of bone turnover. Nonetheless, HRT can

Table 2. Prevention of postmenopausal osteoporosis: "Classical" minimum effective estrogen dosages

Prevention of postmenopausal osteoporosis
Classical minimum dosages of various estrogens used for estrogen-progestagen replacement therapy (indication for low-dose therapy: see text)
Daily minimum effective estrogen dosages

1. Peroral administration:
- 0.625 mg conjugated equine estrogen
- 1.6 mg micronized 17β estradiol
- 2 mg estradiol valerate

2. Transdermal (percutaneous) administration:
- 50 μg 17β estradiol

also offer reliable protection in the later postmenopause [30, 51, 58, 67]. On the other hand, an interruption of replacement results in reactivation of the accelerated bone metabolism, just like before the beginning of replacement [68]. This accelerated bone metabolism again leads to a negative bone balance that may be more or less severe depending on the predisposition, and which ultimately results in postmenopausal osteoporosis with an increased incidence of fracture.

In a comparative study with estrogens plus calcium versus calcium monotherapy, Lindsay et al were able to show in women with a mean time since the menopause of 12 years that after two-year estrogen treatment the bone density in the lumbar spine and in the femoral neck was significantly higher in the group receiving hormone plus calcium than in the group receiving only calcium [30], and that the bone density had actually increased slightly at both sites. Other authors have also pointed out the importance of calcium supplementation [69–71].

More recent data show that bone loss could increase again in older women, mainly in the region of the femoral neck [72], which underlines the importance of osteoporosis prevention in older and old women. In this age group, which usually has the mildest subjective symptoms, mastodynia and other estrogen-induced side effects often have an extremely negative effect on compliance. In older women, good clinical results can usually be achieved with a low-dosed hormone replacement therapy (1 mg 17-beta estradiol or 0.3 mg conjugated estrogens peroral or 25 µg transdermal estradiol) with a lower incidence of side effects (see below) [73–77].

The older woman in particular needs our specific advice and an individual procedure, which is still not realized often enough today. Since there is no upper age limit for the first prescription of hormone replacement therapy, we all have to familiarize ourselves with these problems. New, lower-dosed peroral and transdermal preparation for continuous combined estrogen-progestagen replacement make a major contribution towards facilitating replacement therapy for older women. In order to individualize the hormone treatment in the later menopause, the possibility to administer estrogen locally in the vagina using a ring or a deposit ovulum in women suffering only from urogenital complaints and without any metabolic risk. This option is particularly useful in geriatrics. The fact that it may also be regarded from the aspect of nursing care is often overlooked: Especially in bedridden women, an atrophic mucosa will cause more local discomfort and complaints than a mucosa that is more or less eutrophic thanks to local estrogen administration.

Whether estrogens and progestagens should be administered as osteoporosis prevention for women with breast cancer is currently an issue under discussion. For more information on this issue, the relevant literature should be consulted. According to the valid recommendations, it seems that the administration of estrogens and progestagens to women previously presenting with breast cancer without lymphatic or distant metastasis is possible under certain conditions. If there are no vasomotor complaints, raloxifen (see below) or bisphosphonates can be used. The fact that the anti-estrogen tamoxifen also acts as an osteoprotective agent should be considered. Certain progestagens and the synthetic steroid tibolone have an osteoprotective effect, too. In any case, the oncologist attending the patient should be

consulted before coming to a therapy decision.

LOW-DOSE THERAPY

It is no coincidence that the question of whether the classical dosage guidelines for the well-known estrogen-progestagen preparations that are prescribed immediately after the menopause are really optimal in the later postmenopause is being raised more and more often. An increasing number of colleagues are realizing that those therapeutic regimes that we are familiar with in the first years after the menopause are only conditionally suitable for older women. Especially in older women it is wise to start with a relatively low dose because of the side effects that must otherwise be expected. As more recent studies have shown, such lower dosages are usually sufficient for reliable osteoporosis prevention if the calcium intake is sufficient and there is sufficient physical exercise [73–77]. This is confirmed both by bone density studies and by controls of the biochemical bone markers, which were within the normal range. However, when using such lower dosages the hormone administration must be controlled and monitored individually in order not to overlook non-responders. Especially, but not only in the older woman it has been shown that a low-dose hormone replacement therapy with 1 mg 17-beta estradiol or 0.3 mg conjugated estrogen peroral or 25 µg estradiol transdermal can achieve satisfactory results with few side effects.

The majority of low-dose preparations available today contain a fixed progestagen combination, often norethisterone acetate (NETA).

OSTEOPOROSIS PROPHYLAXIS WITH ESTROGENS AND PROGESTAGENS: HOW LONG?

If administered long enough, HRT not only improves the bone density in postmenopausal women, but also reduces the fracture incidence [7–9]. It has also been shown that an increased bone loss sets in again as soon as the HRT is withdrawn. Thereby, the bone turnover increases again to roughly the values found in untreated women after the menopause [52]. According to other data, however, the acceleration of bone turnover could be slightly lower [24]. These varying results are best explained by the fact that the extent of bone loss can vary depending on genetic predisposition and nutrition habits.

Minimum duration of therapy would appear to be five years or, according to a different opinion, closer to ten years. Too short administration of HRT in the first years after the menopause as treatment for the subjective symptoms does not guarantee long-term protection against osteoporotic fractures. Cohort studies were able to show that long-term prevention reduces the occurrence of spinal deformation in the postmenopause by about 90% [1]. Other data shows that HRT over a period of at least six years reduces the risk of radius and femoral neck fractures by about half.

OSTEOPOROSIS PREVENTION: ALTERNATIVES

In addition to classical HRT, raloxifen (a SERM) or tibolone, both of which

have an action similar to that of estradiol, and bisphosphonates [78–88] can be used for prevention.

Tibolone

Tibolone has partial estrogenic, pro-gestagenic and androgenic effects that are due to its three main metabolites: Tibolone itself may be regarded as a pro-drug. It prevents bone loss and re-stores an increased bone turnover to the normal range. As we and others have shown, the increase in bone den-sity during tibolone treatment is signifi-cant [58, 77, 89]. In addition, tibolone has a beneficial effect on the classical subjective menopause symptoms, and according to the available data it has a favorable effect on the cardiovascular system. Tibolone can also be used for older patients, since it usually leads to amenorrhea.

Selective estrogen receptor modulators (SERMs)

Various SERMs have been developed in recent years. Today, one preparation from this group is available on the market: Raloxifen. Raloxifen acts as an estrogen antagonist in the breast tissue and endometrium, and as an agonist in the bone and in the cardiovascular sys-tem. Available clinical data show that raloxifen has a beneficial effect on bone density. The breast tissue is not stimulated, and the endometrium re-mains atrophic. This action could be of advantage for women with an in-creased risk of breast cancer.

The disadvantage of raloxifen lies in the fact that the vasomotor symptoms are not improved and may even be exacerbated. Therefore, raloxifen is best used for osteoporosis prophylaxis in women without subjective symptoms and in older women.

In younger as in older women, SERMs lead to normalization of the bone turnover and to a certain increase in bone mass [48, 78, 90]. Various other studies confirm the beneficial effect of SERMs in osteoporosis prevention.

Tamoxifen can also be regarded as a SERM. Tamoxifen also acts as an estro-gen agonist in the bone, but unlike raloxifen it has a stimulating effect on the endometrium.

WHO NEEDS HORMONE REPLACEMENT?

Initially, we can base our decision on the list of risk factors that increase the likelihood of osteoporosis. Despite all efforts to eliminate the risk factors, about 30–35 % of all women remain in the group of patients with a high risk of postmenopausal osteoporosis, presum-ably on account of their genetic predis-position. This group is characterized by pathologically high bone turnover, which can be identified by repeated measure-ment of the bone density and the bio-chemical bone markers. Since estrogen

Table 3. Requirements on hormonal replacement therapy with estrogens and progestagens after the menopause

- Elimination of subjective estrogen deficiency symptoms
- Improved quality of life
- Reduction of skin and mucosa atrophy
- Prophylaxis/therapy of postmenopausal osteoporosis
- Reduction of increased risk for cardiovas-cular disease
- Reduction of increased risk for Alzheimer's disease
- No side effects
- Positive individual risk-benefit ratio
- Good acceptance (long-term replacement!)
- Low price

deficiency is the main causal factor in the group of postmenopausal osteoporosis, these women must be identified specifically so that they can benefit from hormone replacement therapy.

Since the first publications by Nordin et al [63], Lindsay et al [30, 64] and Christiansen et al [52, 65], it has been known that estrogen replacement allows the high fracture rate to be reduced to a normal level. On the other hand, senile osteoporosis cannot be prevented by hormone replacement alone. As shown above, however, the estrogen deficiency can be partly responsible for further bone loss, even at higher ages. We know today that there are no age limits for starting osteoporosis prophylaxis with sexual steroids: A woman can still benefit from hormone replacement therapy that is started ten or more years after the menopause, if she is going through a phase with increased bone turnover. It is also accepted that a certain degree of bone regeneration can be induced with hormone replacement, even though it is very limited. Even in women with manifest clinical osteoporosis, the bone density of the spine and the femoral neck can still increase by 2–3 % per year, if estrogens and progestagens are administered in the correct dosage [31]. Whilst estrogens act mainly in the trabecular bones and less in the cortical bones, it would seem that certain progestagens and tibolone also protect the cortical bone [32–34].

In addition to the indication "prevention of osteoporosis", we should not forget all the other classical indications for hormone replacement (Table 4). Women who are already receiving correct estrogen-gestagen replacement for another indication usually do not require densitometric monitoring of the bone density. This is reserved for those cases in which the initial bone mass measurement determines whether they have sufficient bone mass or may belong to the osteoporosis risk group and therefore require hormone replacement. However, the following two basic principles must always be observed:

1. The bone density that is measured in one skeletal region does not allow safe conclusions to be drawn with regard to the bone density in other skeletal regions and thus a global assessment of the fracture risk, especially where a bone of a different skeletal type is concerned [22–25].

2. Osteoporosis is only one of several indications for hormone replacement therapy. The decision for or against replacement therapy should never be based on the bone status alone.

PRACTICAL PROCEDURE

Of the therapy variants shown in Figure 1, cyclical-sequential administration is mainly used immediately before and after the menopause. The second vari-

Table 4. Indications for postmenopausal hormone replacement therapy with estrogens and progestagens

- Primary ovarian insufficiency before the age of 50
- Existing osteoporosis/reduced bone density/pathological biochemical markers
- Neurovegetative dystonia
- Dysphorias/depressive condition
- Urogenital atrophy
- Sexual steroid-related disorders of the sexuality
- High familial risk of osteoporosis
- Cardiovascular prophylaxis in cases with increased personal or familial risk
- Muscle, joint and back pain
- Skin atrophy
- Atrophy of the mucosa
- Increased risk of Alzheimer's disease

ant, sequential administration without interruption of estrogen administration is used mainly within the first 3–5 years after menopause. However, it is also possible to continue prescribing this regime for older women, if the regular menstrual bleeding that follows the progestagen phase is accepted, but most older women tend to prefer daily concurrent administration of an estrogen and a progestagen, which usually results in amenorrhea. Thereby, the recurrence of menstrual bleeding is avoided after the first 3–6 months, during which irregular bleeding can still be observed. The patient must however be informed that unpredictable irregular bleeding is common in the beginning.

Altogether, there are only few cases in which peroral administration or transdermal hormone administration is clearly the presentation form of choice due to clear medical indications, in order to either intentionally achieve or intentionally avoid a first-pass effect.

Fractures as a consequence of the onset of osteoporosis are not always the result of a reduced peak bone mass alone, or of deficient estrogen secretion after the menopause. Especially in older patients that do not spend much time out of doors and have very little exposure to sunlight, it is important to check whether the minimum 1,25-dihydroxy-vitamin D levels are guaranteed. In older people, this is commonly not the case [10], so that combined replacement with calcium and vitamin D must be provided. Tillyard et al [62] have used the active form of vitamin D3, calcitriol, with good therapeutic success. Normally, however, calcitriol should be reserved for patients with a 1,25-hydroxylase deficiency who cannot transform the inactive vitamin D3 contained in their nutrition. It is a matter of course that in addition to any hormone replacement a sensible nutrition and lifestyle that avoids the risk factors and includes plenty of physical exercise is extremely important. A balanced diet with sufficient calcium intake, sufficient physical exercise, and refraining from excessive smoking or alcohol intake clearly improves the

THERAPY REGIMES   ■ **ESTROGENS**
    ▨ **PROGESTAGENS**

a) sequential-interrupted
1   21   28/1   21 days
    10–12   21   10–12   21 days

b) sequential-uninterrupted
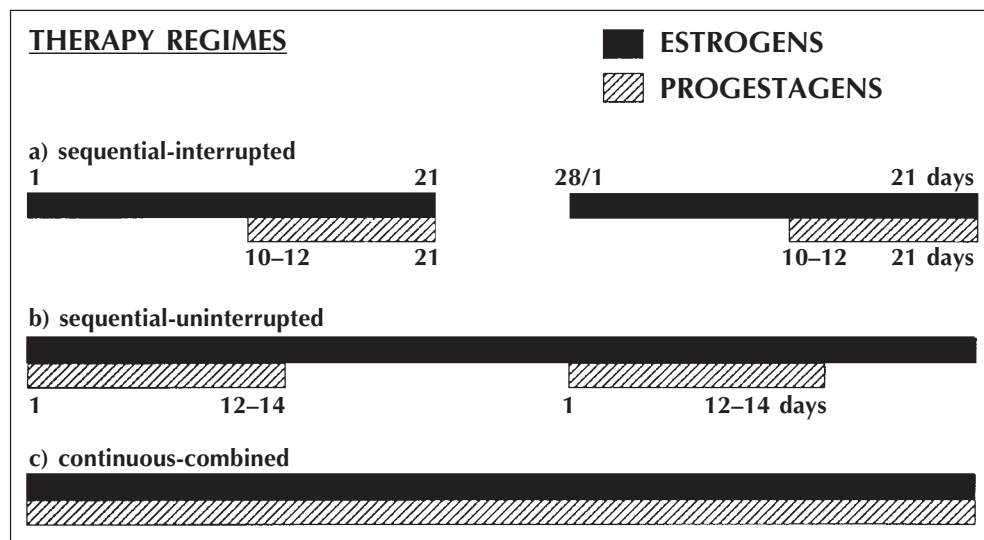1   12–14   1   12–14 days

c) continuous-combined

Figure 1. Estrogen-progestagen replacement after the menopause: the three basic types

chances of preserving a good bone density even in old age.

Last but not least, the fracture risk is determined not only by the bone mass alone, but also by the tendency to fall, which can be reduced by specific training to improve balance, whereby regular gymnastics up to old age are helpful. The fall risk can also be reduced by avoiding unnecessary sleeping pills and sedatives, and by checking the homes of elderly people for typical stumbling stones such as loose electrical wiring or folds in carpets.

SIDE EFFECTS AND RISKS

Since hormone replacement must be continued for a period of at least 15–30 years in order to be able to achieve the metabolic benefits in the bone and in the cardiovascular system, every woman must be aware of the side effects and possible risks of long-term treatment. Most of the side effects are harmless and usually disappear again if the administration form or the type of estrogen or progestagen is changed. In principle, the perfect hormone combination can be found for every woman.

The weight increase that is frequently feared is about 300 g on average, taking our own data into account. Basically, it can be put down to rehydration of the tissue, which is secondary to estrogen administration. A weight gain in excess of 800 g is often incorrectly attributed to the hormone therapy itself, but usually it is independent of exogenous hormones and is due to a general change in metabolism. It must be borne in mind that certain progestagens can stimulate the appetite, so that the patient eats more without realizing it. Moreover, it must always be

considered that changes in carbohydrate metabolism with insulin resistance are possible around the time of the menopause, although largely independent thereof.

In a healthy patient, arterial hypertension will not be caused by hormone replacement. In fact, hormone replacement will actually lower the mean blood pressure slightly.

Although the metabolic benefits, like the improvement of subjective climacteric symptoms, have been acknowledged by virtually everyone, we known that more than 50% of all women discontinue their hormone replacement therapy after one year, and that a maximum of 200 out of 1000 patients are still on hormone replacement therapy after 10 years.

The reason for this poor therapy adherence is probably the unadmitted fear of possible side effects and risks. Even if hormone replacement therapy is regarded as a routine treatment nowadays, many women still have doubts about the risk-benefit ratio of long-term therapy that can only be removed with well-founded and precise information. In particular, this applies to the issue of carcinoma due to HRT, an extremely important topic that will be dealt with in a separate chapter.

BIBLIOGRAPHY

1. Albright F, Smith PH, Richardson AM. Post-menopausal osteoporosis: Its clinical features. JAMA 1941; 116: 2465.
2. Seeman E, Hopper JL, Bach LA, Cooper ME, Parkinson E, McKay J, Jerums G. Reduced bone mass in daughters of women with osteoporosis. New Engl J Med 1989; 320: 554.
3. Slemenda CW, Christian JC, Williams CJ, Norton JA, Johnston Jr CC. Genetic determinants of bone mass in adult women: a re-evaluation of the twin model and the potential importance of gene interaction on heritability estimates. J Bone Miner Res 1991; 6: 561.
4. Theitz G, Buch B, Rizzoli R, Slosman D, Clavien H, Sizonko PC, Bonjour JPH. Longitudinal monitoring of bone mass accumula-

tion in healthy adolescents: evidence for a marked reduction after 16 years of age at the levels of lumbar spine and femoral neck in female subjects. J Clin Endocrinol Metab 1992; 75: 1060.

5. Matkovic V, Jelic T, Wardlaw GM, Ilich J, Goel PK, Wright JK, Andon MB, Smith KT, Heaney RP. Timing of peak bone mass in caucasian females and its implications for the prevention of osteoporosis: interference from a cross-sectional model. J Clin Invest 1994; 93: 799.

6. Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB. Bone gain in young women. JAMA 1992; 268: 2403.

7. Ettinger B, Sidney S, Cummings SR, Libanati C, Bikle DD, Tekawa IS, Tolan K, Steiger P. Racial differences in bone density between young adult black and white subjects persist after adjustment for anthropometric, lifestyle, and biochemical differences. J Clin Endocrinol Metab 1997; 82: 429.

8. Nelson DA, Simpson PM, Johnson CC, Barondess DA, Kleerekopper M. The accumulation of whole body skeletal mass in third- and fourth-grade children: effects of age, ethnicity, and body composition. Bone 1997; 20: 73.

9. Hopper JL, Seeman E. The bone density of female twins discordant for tobacco use. New Engl J Med 1994; 330: 387.

10. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D3 and calcium to prevent hip fractures in elderly women. New Engl J Med 1992; 327: 1637.

11. Cummings SR, Nevitt MC, Ettinger B, Stone K, Fox KM, Ensrud KE, Cauley J, Black D, Voigt TM. Risk factors for hip fracture in white women. Study of Osteoporotic Fracture Research Group. New Engl J Med 1995; 332: 767.

12. Chow RK, Harrison JE, Brown CF, Hajek V. Physical fitness effect on bone mass in postmenopausal women. Arch Phys Med Rehab 1986; 67: 231.

13. Dalsky G, Stocke KS, Ehsani AA, Slatopolsky E, Lee WC, Birjes Jr J. Weight-bearing exercise training and lumbar bone mineral content in postmenopausal women. Ann Intern Med 1988; 108: 824.

14. Brooke-Wavell K, Jones PRM, Hardman AE. Brisk walking reduces calcaneal bone loss in post-menopausal women. Clin Sci 1997; 92: 75.

15. Lukert BP, Johnson BE, Robinson RG. Estrogen and progesterone replacement therapy reduces glucocorticoid-induced bone loss. J Bone Miner Res 1992; 7: 1063.

16. Hall GM, Daniels M, Doyle DV, Spector TD. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. Arthritis Rheum 1994; 37: 1499.

17. Ettinger B, Genant HK, Steiger P, Madvig P. Low-dosage micronized 17β-estradiol prevents bone loss in postmenopausal women. Am J Obstet Gynecol 1992; 166: 479–88.

18. Naessen T, Persson I, Ljunghall S, Bergstrom R. Women with climacteric symptoms: a target group for prevention of rapid bone loss and osteoporosis. Osteoporosis Int 1992; 2: 225–31.

19. Mazess RB, Barden HS. Interrelationships among bone densitometry sites in normal young women. Bone Miner 1990; 11: 347–56.

20. Turner RT, Rigges BL, Spelsberg TC. Skeletal effects of estrogen. Endocr Rev 1994; 15: 275.

21. Liel Y, Kraus S, Levy J, Shany S. Evidence that estrogens modulate activity and increase the number of 1,25-dihydroxyvitamin D receptors in osteoblast-like cells (ROS 17/2,8). Endocrinology 1992; 130: 2597.

22. Lindsay R. Sex steroids in the pathogenesis and prevention of osteoporosis. In: Riggs BI (ed.). Osteoporosis: Etiology, Diagnosis and Management. Raven Press New York, 1988; 333–45.

23. Ettinger B, Genant HK, Cann CE. Postmenopausal bone loss is prevented by treatment with low dosage estrogen with calcium. Ann Intern Med 1987; 106: 40–6.

24. Lindsay R, Hart DM, Forrest C, Baird C. Prevention of spinal osteoporosis in oophorectomized women. Lancet 1980; 2: 1151–4.

25. Garnett T, Studd J, Watson N, Savvas M, Leather A. The effects of plasma estradiol levels on increases in vertebral and fernoral bone density following therapy with estradiol and estradiol with testosterone implants. Obstet Gynecol 1992; 79: 968–72.

26. Hänggi W, Casez JP, Birkhäuser MH. Der Einfluß längerdauernder Amenorrhoe auf die Knochendichte der jungen Frau. Arch Gynaecol Obstet 1991; 249 (Suppl): 127.

27. Weiss NS, Ure CL, Ballard JH, Williams AR, Dalin JR. Decreased risk of fractures of the hip and lower forearm with postmenopausal use of estrogen. N Engl J Med 1980; 303: 1195–8.

28. Kiel DP, Felson DT, Andersen JJ, Wilson PWF, Moskowitz MA. Hip fracture and the use of estrogens in postmenopausal women. The Framingham study. N Engl J Med 1987; 317: 1169–74.

29. Consensus Development. Diagnosis, prophylaxis and treatment of osteoporosis. Am J Med 1993; 94: 646–50.

30. Lindsay R, Aitken JM, Andersen JB, Hart DMM, MacDonald EB, Clarke AC. Long-term prevention of postmenopausal osteoporosis by oestrogen. Lancet 1976; I: 1038–40.

31. Abdalla HI, Hart DM, Lindsay R, Leggate I, Hooke A. Prevention of bone mineral loss in postmenopausal women by norethisterone. Obstet Gynecol 1985; 66: 789–92.

32. Lindsay R, Hart DM, Purdie D, Ferguson MM, Clark AS, Kraszewski A. Comparative effects of estrogen and a progestogen on bone loss in postmenopausal women. Clin Sci 1978; 54: 193–5.

33. Riis BJ, Christansen C, Johansen JS, Jacobsen J. Is it possible to prevent the bone loss in young women treated with a LH-RH agonist? J Clin Endocrinol Metab 1997; 70: 920–4.

34. Drinkwater BL, Nilson K, Chesnut CH III, Bremner WJ, Shainholtz S, Southworth MB. Bone mineral content of amenorrhoeic and eumenorrhoeic athletes. N Engl J Med 1984; 31: 277.

35. Haenggi W, Casez JP, Birkhaeuser MH, Lippuner K, Jaeger Ph. Bone mineral density in young women with longstanding amenorrhea: limited effects of hormone replacement therapy with ethinylestradiol and desogestrel. Osteoporosis Int 1994; 4: 99–103.

36. Nilas L, Christiansen C. Bone mass and its relationship to age and the menopause. J Clin Endocrinol Metab 1987; 65: 697–702.

37. Richelson LS, Wahner HW, Melton III LJ, Riggs BL. Relative contributions of aging and estrogen deficiency to postmenopausal bone loss. N Engl J Med 1984; 311: 1273–5.

38. Smith DM, Khairi MRA, Norton J, Johnston CCj. Age and activity effects on rate of bone mineral loss. J Clin Invest 1976; 58: 716–21.

39. Jensen GJ, Christiansen C, Boesen J, Hegedus V, Transbol F. Epidemiology of postmenopausal spinal and long bone fractures: a unifying approach to postmenopausal osteoporosis. Clin Orthop 1982; 166: 75–81.

40. Riggs BL, Wahner HW, Seeman E, Offord KF, Dunn WL, Mazes RB, Johnston K, Melton LJ. Changes in bone mineral density of the proximal femur and spine with aging: Differences between the postmenopausal and senile osteoporosis syndrome. J Clin Invest 1982; 70: 716–23.

41. Mazess RB, Barden H, Ettinger M, Schulz E. Bone density of the radius, spine and proximal femur in osteoporosis. J Bone Miner Res 1988; 3: 13–8.

42. Cummings SR, Black DM, Nevitt Mc, Browner W, Cauley J, Ensrud K, Genant HK, Palermo L, Scott J, Vogt TM. Bone density at various sites for prediction of hip fractures. Lancet 1993; 341: 72–5.

43. Adashi EY. The climacteric ovary as a functional gonadotropin-driven androgen-producing gland: Fertil Steril 1994; 62: 20.

44. Melton LJ, Kan SH, Wainer HW, Riggs BL. Lifetime fracture risk: An approach to hip fracture risk assessment based on bone mineral density and age. J Clin Epidemiol 1988; 41: 985–94.

45. Palummeri E, Gelmini G, Bonati PA, Bergonzani M, Davoli L. Effect of ovariectomy on bone mass. Transverse study using photon densitometry. Minerva Ginecol 1987; 39: 607–13.

46. Ott SM. Bone density in adolescents. N Engl J Med 1991; 325: 1646–7.

47. Hassager C, Jensen LT, Johansen JS, Riis BJ, Melkko J, Podenphant J, Risteli L, Christiansen C, Risteli J. The carboxy-terminal propetide of type 1 procollagen in serum as a marker of a bone formation: the effect of nandrolone decanoate and female sex hormones. Metabolism 1991; 40: 205–8.

48. Pouillés JM, Trémollières F, Ribot C. The effects of menopause on longitudinal bone loss from the spine. Calcif Tissue Int 1993; 52: 340–3.

49. Genant HK, Faulkner KG, Glüer CC, Engelke K. Bone densitometry: current assessment. Osteoporosis Int 1993; 3 (Suppl. 1): 91–7.

50. Christiansen C. Diagnosing the risk of osteoporosis – the modern approach. In: Riggs BL (ed.). Prevention and treatment of osteoporosis. Hogrefe & Huber Publishers Lewiston-Toronto-Bern-Göttingen, 1992; 21–9.

51. Riis BJ, Thomsen K, Strom V, Christiansen C. The effect of percutaneous estradiol and natural progesterone on bone loss. Am J Obstet Gynecol 1987; 156: 61–5.

52. Christiansen C, Christensen MS, Transbol I. Bone mass in postmenopausal women after withdrawal of estrogen/gestagen replacement therapy. Lancet 1981; I: 459–46.

53. Riis BJ, Jensen JJ, Christiansen C. Cyproteronacetate, an alternative gestagen in postmenopausal estrogen/gestagen therapy? Clin Endocrinol 1987; 26: 327–34.

54. Lufkin EG, Wahner HW, O'Fallon WM et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992; 117: 1–9.

55. Gotfredsen A, Niklas L, Riis BJ, Thomsen K, Christiansen C. Bone changes occurring spontaneously and caused by oestrogen in early postmenopausal women: a local or generalized phenomenon? Br Med J 1986; 1098–100.

56. Riis BJ, Christiansen C. Measurement of spinal or peripheral bone mass to estimate early postmenopausal bone loss? Am J Med 1988; 84: 646–53.

57. Ribot C, Trémollières F, Pouillés JM. Cyclic Estraderm TTS 50 plus oral progestogen in the prevention of postmenopausal bone loss over 24 months. In: Christiansen C, Overgaard K (eds). Osteoporosis, Vol. 2. Osteopress, Copenhagen 1990.

58. Lippuner K, Haenggi W, Birkhaeuser MH, Casez J-P, Jaeger P. Prevention of postmenopausal bone loss using tibolone or conventional peroral or transdermal hormone replacement therapy with 17-beta-estradiol and dydrogesterone. J Bone Miner Res 1997; 12: 806.

59. Stevenson JC, Cust MP, Gangar KF, Hillard TC, Lees B, Whitehead MI. Effects of transdermal versus oral hormone replacement

therapy on bone density in spine and proximal femur in postmenopausal women. Lancet 1990; 336: 265–9.

60. Ribot C, Trémollières F, Poullés JM, Louvet JP, Peyron R. Transdermal administration of 17β-estradiol in postmenopausal women: Preliminary results of a longitudinal study. In: Christiansen C, Johansen JS, Riis BJ (eds). Osteoporosis. Osteopress, Kopenhagen, 1987; 1.

61. Studd J, Savvas M, Waston N, Garnett T, Fogelman I, Cooper D. The relationship between plasma estradiol and the increase in bone density in postmenopausal women after treatment with subcutaneous hormone implants. Am J Obstet Gynecol 1990; 163: 1474–9.

62. Tillyard MW, Spears GFS, Thomson J, Dovey S. Treatment of postmenopausal osteoporosis with calcitriol or calcium. New Engl J Med 1992; 326: 357–62.

63. Nordin BEC, Horshman A, Crilly RG, Marshall DH, Simpson M. Treatment of spinal osteoporosis in postmenopausal women. Br Med J 1980; 280: 451.

64. Lindsay R, Tohme JF. Alterations in skeletal homeostasis with age and menopause. In: Mishell DR (ed.). Menopause: Physiology and Pharmacology. Year Book Medical Publishers Inc. Chicago, London, 1987; 165.

65. Christiansen C, Christensen MS, McNair P, Hagen PC, Stocklund KE, Transbol IB. Prevention of early postmenopausal bone loss: controlled study in 315 normal females. Eur J Clin Invest 1987; 10: 273.

66. Grey AB, Cundy TF, Reid IR. Continuous combined oestrogen/progestin therapy is well tolerated and increases bone density of the hip and spine in postmenopausal osteoporosis. Clin Endocrinol 1994; 40: 671–7.

67. Christiansen C, Riis BJ. 17-beta-Estradiol and continuous norethisterone: a unique treatment of established osteoporosis in elderly women. J Clin Endocrinol Metab 1990; 71: 836–41.

68. Lindsay R, Hart DM, Maclean A, Clark AC, Kraszewski A, Garnwood J. Bone response to termination of estrogen treatment. Lancet 1978; 1: 1321–7.

69. Riis BJ, Thomsen K, Christansen C. Does calcium supplementation prevent postmenopausal bone loss; a double-blind controlled clinical study. N Engl J Med 1987; 316: 173–7.

70. Ettinger B, Genant HK, Cann CE. Postmenopausal bone loss is prevented by treatment with low-dosage estrogen with calcium. Ann Intern Med 1987; 104: 40–4.

71. Riis BJ, Nilas L, Christiansen C. Does calcium potentiate the effect of estrogen therapy on postmenopausal bone loss? Bone Miner 1987; 2: 1–5.

72. Black DM. Why elderly women should be screened and treated to prevent osteoporosis. Am J Med 1995; 98 (2A): 67S–75S.

73. Evans SF, Davie MWJ. Low and conventional dose transdermal oestradiol is equally effective at preventing bone loss in spine and femur at all post-menopausal ages. Clin Endocrinol 1996; 44: 79–84.

74. Sharp CA, Evans SF, Davie MWJ et al. Effects of low- and conventional-dose transcutaneous HRT over 2 years on bone metabolism in younger and older postmenopausal women. Eur J Clin Invest 1996; 26: 763–71.

75. Bjarnason NH, Hassager C, Christiansen C. 17-beta-Estradiol 1 mg and 2 mg oral combinations with a new gestagen, gestoden, are equally preventive for bone loss in early postmenopausal women. Bone 1997; 20: 93S.

76. Bjarnason NH, Hassager C, Christansen C. Profile of a new substitution principle: Low dose 17-beta-estradiol and gestodene. Acta Obstet Gynecol Scand 1997; 76 (Suppl 167): S56.

77. Stadberg E, Mattson L-C, Uvebrant M. Low doses 17-beta-estradiol and norethisterone acetate as continuous combined hormone replacement therapy in postmenopausal women: Lipid metabolic effects. Menopause 1996; 3: 90–6.

78. Ke HZ, Chidsey-Frink KL, Oi H et al. Droloxifene increases bone mass in ovariectomized rats with established osteopenia. J Bone Miner Res 1997; 12 (Suppl 1): S349.

79. Black DM, Cummings SR, Karpf DB et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fracture. Fracture intervention trial research group. Lancet 1996; 348: 1535–41.

80. Cummings SR, Black DM, Thompson DE, For the FIT research group. Alendronate reduces the risk of vertebral fractures in women without pre-existing vertebral fractures: Results of the fracture intervention trial. J Bone Miner Res 1997; 12 (Suppl 1): S149.

81. Storm TM, Thamsborg G, Steiniche T, Genant HK, Sorensen OM. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990; 322: 1265–71.

82. Meunier PJ, Confavreux E, Tupinon I, Hardouin C, Delmas PD, Balena R. Prevention of early postmenopausal bone loss with cyclical etidronate therapy (a double-blind, placebo-controlled study and 1-year followup), J Clin Endocrinol Metab 1997; 82: 2784.

83. Stock JL, Bell NH, Chesnut III CH, Ensrud RE, Genant HK, McClung MR, Singes FR, Yood RA, Pryor-Tillotson S, Weil L, Santora II AC. Increments in bone mineral density of the lumbar spine and hip and suppression of bone turnover are maintained after discontinuation of alendronate in postmenopausal women. Am J Med 1997; 103: 291.

84. Karpf DB, Shapiro DR, Seeman E, Ensrud KE, Johnston Jr CC, Adami S, Harris ST, Santora II AC, Hirsch LJ, Oppenheimer L, Thompson D, for the Alendronate Osteoporosis Treatment Study Group. Prevention of nonvertebral fractures by alendronate. JAMA 1997; 277: 1159.

85. Hoskins D, Chilvers CED, Christiansen C, Ravn P, Wasnich R, Ross P, McClung M, Balske A, Thompson D, Daley M, Yates AJ, for the Early Postmenopausal Intervention Cohort Study Group. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. New Engl J Med 1998; 338: 485.

86. Weiss S, McClung M, Gilchrist N et al. Five-years efficacy and safety of oral alendronate for prevention of osteoporosis in early post-menopausal women. J Bone Miner Res 1997; 12 (Suppl 1): S144.

87. McClung M, Clemmesen B, Daifotis A, Gilchrist NL, Eisman J, Weinstein RS, Fuleihan GEH, Reda C, Yates AJ, Ravn P, for the Alendronate Osteoporosis Prevention Study Group. Alendronate prevents postmenopausal bone loss in women without osteoporosis: a double-blind, randomized, controlled trial, Ann Intern Med 1998; 128: 253.

88. Lufkin EG, Whitaker R, Argueta R, Caplan RH, Nickelsen T, Riggs BL. Raloxifene treatment of postmenopausal osteoporosis. J Bone Miner Res 1997; 12 (Suppl 1): S150.

89. Bjarnason NH, Bjarnason K, Haarbo J, Rosenquist C, Christiansen C. Tibolone prevention of bone loss in late postmenopausal women. J Clin Endocrin Metab 1996; 81: 2419–22.

90. Delmas PD, Bjarnason NH, Mitlak BH, et al. The effects of raloxifene on bone mineral density, serum cholesterol, and unterine endometrium in postmenopausal women. N Engl J Med 1997; 337: 1641–7.

Editor:
Franz H. Fischl

MENOPAUSE
ANDROPAUSE

Hormone replacement therapy through the ages
New cognition and therapy concepts

http://www.kup.at/cd-buch/8-inhalt.html