14.1
Hormone Replacement Therapy for Women – Now Recommended for Symptoms Only!

Decrease in oestrogen production starts well before the menopause and initiates a continuous loss of bone. After the menopause, and in the absence of therapy, 1–4% of the bone mass may be lost annually. In general, the indications for hormone replacement therapy (HRT) used to be:

- Relief of postmenopausal symptoms and signs attributable to oestrogen deficiency
- Reduction of risk of diseases associated with oestrogen deficiency (osteoporosis, cardiovascular and cerebrovascular disorders).
- HRT was thought to delay cognitive decline, but this has not been substantiated.

Long-term use (5–10 years) of oestrogen results in a reduction of fractures of the hip, vertebrae and arm by about 50%. The greatest effect is seen in the vertebral column: within 2 years of HRT increases of up to 10% in bone density of the lumbar vertebrae, and up to 4% in the femoral neck have been reported. The effect of HRT is more pronounced in skeletal sites with mainly trabecular bone. On cessation of HRT, bone loss resumes at the postmenopausal rate.

A significant reduction in the incidence of fractures had occurred in the years during which HRT was widely taken, confirmed by many studies, for example from Norway. In contrast, other studies, one from Australia, showed a decrease in the incidence of breast cancer after the decrease in use of HRT. Other analyses of mainly European women showed that many who had been on HRT switched to bisphosphonates and/or raloxifene, as described in a French study. Raloxifene is the only selective oestrogen receptor modulator (SERM) that has been officially approved and covered by insurances in some countries, such as Japan, for the prevention and management of osteoporosis.

Although oestrogen is considered to be the gold standard for osteoporosis prevention, not all patients experience an increase in bone mass. Because of this, the National Osteoporosis Foundation recommends bone mineral density (BMD) testing for all women on long-term HRT to assure that patients have responded to this treatment. In patients who have not responded adequately to oestrogen therapy (also referred to as ERT when only oestrogen is used) or in those found to have a low bone mass, a combination of HRT and alendronate has additive benefits on bone and could be considered, together with anabolic therapy with parathyroid hormone (PTH). Every woman who reaches the menopause is therefore confronted with the far-reaching decision as to whether or not to begin HRT. It is advisable to reach a decision concerning HRT and ERT only after consultation with the patient and a gynaecologist.

A BMD measurement and evaluation of the patient’s risk profile, including family history, also contribute to the decision. But today, the indications are far more limited and the operative principles are:

- Who should get HRT? – As few women as possible.
- How much HRT? – As little as possible.
- For how long? – As short as possible.

The mechanisms of action of oestrogen on bone and tissues related to maintenance of bone are complex and include (Figs. 14.1 and 14.2):
14.2 Which Oestrogens and Progestins, and How to Take Them?

The main groups of oestrogen preparations given orally or transdermally are:

- Synthetic oestrogen analogues with a steroid skeleton
- Non-human oestrogen, produced from an equine source (conjugated equine oestrogens)
- Native human oestrogens or compounds that are transformed to native oestrogens in the body

Effective daily doses of commonly used oestrogens are:

- Oestradiol Orally 2 mg
- Patch 50 µg
- Gel 1 mg
- Conjugated equine oestrogens 0.625 mg
- Oestradiol valerate 2 mg

For women with an intact uterus, oestrogen should be combined with progestin to prevent the risk of endometrial hyperplasia and cancer. Cyclic treatment is recommended for women immediately after the

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**Fig. 14.1.** Changes in resorption and formation and in bone mass before and at the menopause, without therapy

**Fig. 14.2.** Preservation and/or increase in bone mass, decrease in bone turnover at and after the menopause under the influence of bisphosphonate therapy

- Induction of FasL in osteoblasts, leading to apoptosis in preosteoclasts
- Inhibition of osteoclast activity
- Stimulation of collagen synthesis by osteoblasts
- Promotion of gastrointestinal absorption of calcium
- Stimulation of calcitonin secretion
- Modulation of PTH secretion
- Improvement of central nervous functions and therefore decrease in tendency to fall
- Increased blood flow through the bones

The data from the oestrogen/progesterone arm of the *Women’s Health Initiative (WHI) Study (2003)* has influenced perceptions on the effects of HRT and its role in patient management. The study confirmed that HRT reduces the risk of vertebral, non-vertebral and hip fractures. This was a major advance in the evidence base concerning the effects of HRT on bone, but at the same time, cardiovascular and breast cancer data from the trial have had a negative effect on perceptions and, as a consequence, the use of HRT and ERT is now strictly limited. This is all the more so, as alternatives are readily available and do not have the potentially dangerous side effects of HRT and ERT. As a result, women who do use HRT, limit their use to a short time after the menopause. Women at high risk of osteoporosis who wish to minimize postmenopausal bone loss now have the option of transferring to raloxifene or a nitrogen-containing bisphosphonate, or the combination of the two, as well as the latest anabolic therapy, if osteoporosis is already established.