16.1 A Brief Overview of SERMs – New Selective Antiresorptive Agents

In the last decade, more and more oestrogen-like substances have been developed and introduced into clinical practice. These drugs bind to the oestrogen receptors (ERs alpha and beta) throughout the body. For example tamoxifen had long been given to women with a history of breast cancer, after the initial chemotherapy and radiotherapy and surgery. It acts as an oestrogen antagonist on breast tissue but as an oestrogen on other organs and tissues in the body, namely bone, liver and fat. Tamoxifen inhibits growth of any residual breast cancer cells remaining in the body if they still have oestrogen receptors. However, due to adverse effects, tamoxifen has been replaced by the aromatase inhibitors, for example anastrozole.

16.2 Raloxifene – Utilization of Physiological Effects on Bone

The positive effect on bone has been further developed in raloxifene, a selective oestrogen-receptor modulator (SERM) of the second generation which has no effect on breast or uterus. Raloxifene was originally investigated as a treatment for breast cancer. Uterine bleeding, breast tenderness and water retention are not observed with raloxifene. However, “hot flushes” and leg cramps occurred in about 30% of previously asymptomatic patients, because raloxifene blocks all oestrogen receptors remaining in the body and thereby also the effects of the small amount of oestrogen that might still be produced. Leg cramps, especially nocturnal, can be treated by supplements of magnesium which is freely available; the recommended amount is 300 mg daily. An international clinical trial, the MORE study, showed that the risk of a vertebral fracture in patients taking raloxifene is half that of a control group. After 3 years, raloxifene 60 mg daily increased the BMD by 2–3% at the hips and spine and reduced the risk of new fractures by 30–50%. New clinical vertebral fractures were reduced by 68% after 1-year of therapy with raloxifene. The risk of breast cancer is significantly reduced (60–70%) in women taking raloxifene. This effect was mainly due to a 90% reduction of oestrogen-receptor-positive breast cancer. The RUTH trial is evaluating this positive effect.

The SERMs exert their effects by binding with high affinity to the oestrogen receptors (ERs) of which two different subtypes have so far been identified (ER-alpha and ER-beta) (Fig. 16.1). These receptor subtypes appear throughout the body with a predominance of ER-alpha expression in the reproductive tissues and a predominance of ER-beta expression in non-reproductive tissues. The structural features of each SERM differ so that unique ligand-induced changes take place in the ERs, which are thought to be the likely basis for tissue-selective pharmacology. For example, raloxifene operates as an oestrogen agonist in bone but as an antagonist in the breast and uterus. The mechanism by which SERMs inhibit bone resorption is likely to be the same as that of oestrogen, i.e. by blocking production of cytokines that promote osteoclast differentiation and...
by stimulating TGF-beta3 that suppresses osteoclast activation, while osteoclastic resorption is inhibited by modulation of the OPG-RANKL system. Raloxifene decreases serum levels of OPG and RANKL, so that these levels can be compared to levels of the markers of bone resorption. TGF-beta3 also decreases expression of IL-6 which stimulates bone resorption. Raloxifene probably also acts on osteocytes, which participate in regulation of the maintenance of bone. This physiological pathway of action leads to a completely normal bone structure without mineralization defects or increased numbers of microcracks. Studies of the pharmacokinetics of SERMs have shown considerable differences in their bioavailability. Hepatic, but not renal, impairment affects their metabolism and there is a possibility of interaction with other agents such as warfarin and aromatase inhibitors. The main contraindication of raloxifene therapy is a previous history of thromboembolism since studies have shown an increased incidence of thromboembolism in patients treated with raloxifene. One trial has shown that raloxifene improves renal function in postmenopausal women with diabetes. Raloxifene also reduces the levels of various plasma lipids and increases that of adiponectin; it slows the progression of atherosclerosis. The effects of raloxifene in postmenopausal women with chronic kidney disease (CKD) were investigated in a multicentre randomized, 3-year controlled trial of 7705 postmenopausal women with osteoporosis. Adverse effects in each category of kidney function were the same in the treatment and control groups. The bone mineral density (BMD) at the spine and the hip was increased and the risk for vertebral fractures in the patients with CKD was reduced in the patients on raloxifene therapy.

In summary, SERMs now constitute a new approach to therapy and have been approved for the prevention and treatment of postmenopausal osteoporosis while decreasing the risks of cardiac and circulatory disorders without the unwanted side effects and risks associated with hormone replacement therapy. Raloxifene is considered to be suitable for older women, but its possible side effects must be taken into account and the patients must be informed. In a recent study, SERMs have also been tried in men and the results are awaited soon. Recommended dosage: 60 mg raloxifene (Evista®) orally daily, without restrictions as to when the drug should be taken, but preferably with supplements of vitamin D and calcium. Raloxifene is the treatment of choice for postmenopausal women, especially women with one or more of the following factors:

- High risk for breast cancer or cardiovascular diseases
- High risk of vertebral fractures
- Modest degrees of osteopenia in the postmenopausal period (age 55–65)
- Osteoporosis diagnosed by DXA in the postmenopausal period (age 55–65)

A recent study was undertaken to investigate the efficacy of raloxifene and tibolone on a number of pa-