Role of Oestrogen Deficiency in Osteoporosis in Post-menopausal Rheumatoid Arthritis

a report by

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In post-menopausal rheumatoid arthritis (RA), oestrogen deficiency and inflammatory disease contribute to the development of localised and generalised osteopenia. This leads to an increased risk of fracture, with enhanced morbidity and mortality. More than 50% of women with post-menopausal RA have osteoporosis. Hormone replacement therapy (HRT) is used to treat post-menopausal osteoporosis and compensate for the loss of natural hormones, but is no longer recommended for long-term therapy due to the risk of serious side effects. HRT has also been shown to ameliorate RA, with decreased joint destruction, reduced inflammation, increased bone density and better patient health assessment. This article aims to describe what is known today about the role of oestrogen deficiency in the complex mechanisms leading to the development of osteoporosis in post-menopausal RA.

RA is a common, progressive, systemic autoimmune disease with a prevalence of 0.5–1%. Several findings indicate the involvement of sex hormones in the development and disease course of RA. For example, the female-to-male incidence ratio is 4–5:1 in those below 50 years of age and 2:1 for patients with a later onset. The peak incidence in men occurs at 60–70 years of age, coinciding with the fall in serum levels of biologically active testosterone. Several studies have shown that oestrogen can affect the disease course in RA in humans and animal models. Mice subjected to ovariectomy display higher frequency and increased severity of collagen-induced arthritis (CIA) compared with sham-operated mice. Exposure to oral contraceptives has been shown to reduce the risk of developing RA.

In many women with RA the disease activity diminishes during pregnancy when the levels of female sex hormones are high. In contrast, the disease is often aggravated after delivery. The same effects have also been found in arthritic mice. Breast-feeding has been shown to increase the risk of RA, which may be due to the pro-inflammatory effects of prolactin.

Use of non-contraceptive hormones in the peri-menopausal period was negatively correlated to development of RA in a study of 490 women with RA and controls. Some later studies failed to confirm this. The use of HRT has been associated with some beneficial effects on disease activity. A prospective two-year trial of 88 post-menopausal women with RA found that HRT (2mg oestradiol and 1mg noretisterone) ameliorated clinical disease, retarded joint destruction and increased bone mineral density (BMD). Oestriol treatment of CIA in mice also suppressed disease progression, and blocking of the oestrogen receptors (ORs) enhanced the disease. Treatment of CIA in ovariectomised mice with the selective OR modulator (SORM) raloxifene was also found to ameliorate the clinical disease, bone erosions and the development of osteoporosis. The effect of raloxifene in post-menopausal RA has not yet been evaluated. Raloxifene binds with high affinity to ORα, and acts as an oestrogen agonist in bone and on serum lipids but as an antagonist in breast and uterine tissue. It is approved as treatment for post-menopausal osteoporosis. RA is characterised by different skeletal manifestations, including bone erosions, peri-articular osteopenia and generalised osteoporosis. In post-menopausal RA the prevalence of generalised osteoporosis is increased. In one study, as many as 56% of patients had osteoporosis, resulting in increased risk of fractures. BMD was also found to be reduced in men with RA compared with a healthy reference population. Increasing age, low bodyweight, severe joint destructions and cumulative dose of glucocorticosteroids have been found to be important determinants of reduced BMD in post-menopausal RA.

Oestrogen

The female sex hormone oestrogen has many physiological effects, affecting the development and maturation of the reproductive system, the skeleton and the immune, nervous and cardiovascular systems. There are three different oestrogens in humans: oestrone, oestradiol and oestriol. Oestradiol (O2) is the most potent hormone. It is produced by the granulosa cells of the ovary and to some degree by the adrenal cortex, adipose tissue and testicles through aromatisation of testosterone. At menopause, most of the ovarian production of sex hormones ceases, although some production of testosterone, androstendione, dihydroepiandrosterone, oestrone and oestradiol has been shown to be present 10 years later. Ovariectomy of post-menopausal women significantly decreased serum levels of oestrone and testosterone, revealing some remaining ovarian sex hormone production even after menopause. Mice do not lose the production of sex hormones with age, therefore ovariectomy of mice is used to mimic menopause to enable studies of oestrogen deficiency.

Oestrogen and Bone

The classic ORs, ORα and ORβ, are present in osteoblasts, osteocytes, osteoclasts and chondrocytes, mediating oestrogen effects on bone and cartilage. Indeed, the classic transcription pathway has been demonstrated to be activated in osteoblasts, osteocytes and chondrocytes exposed to oestradiol (see Figure 1). The development of post-
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At first there is a phase of rapid bone loss, dominated by increased bone resorption and trabecular thinning, leading to loss of connection between trabeculae. A slower rate of bone loss follows and is sustained, dominated by decreased bone formation and trabecular thinning. Oestrogenic effects on bone are likely to be mediated by both direct effects on the different cells and changes of the cytokine milieu of the bone compartment. The net effects of oestrogen deprivation are increased bone resorption due to a higher number of activated osteoclasts, deeper resorption pits due to increased osteoclast survival and increased bone formation that is not sufficient to compensate for the resorption. The response in bone to strain is decreased by oestrogen deficiency due to reduced OR activity in osteocytes. The production of several cytokines is influenced by menopause. Thus, the serum levels of interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)α and macrophage-colony-stimulating factor (M-CSF) were found to be increased after natural or surgical menopause in women, and decreased upon oestrogen therapy. In early menopausal women it was demonstrated that the expression of the receptor activator of NF-κB ligand (RANKL) was upregulated on T cells, B cells and pre-osteoblastic bone marrow stromal cells. Serum IL-6 levels can predict bone loss in post-menopausal women. Soluble IL-6 receptor increases after menopause, and this increase can be prevented and reversed with HRT. This prevention was recently also reported in women with post-menopausal RA. Ovariectomy also leads to an increase in serum levels of IL-6, IL-7 and TNFα in mice. These cytokines reduce osteoblast activity and inhibit osteoclast formation and inhibit osteoclast apoptosis. The number of osteoclasts and their precursors have been shown to increase after ovariectomy in mice. Indeed, TNFα knockout mice do not develop osteoporosis after ovariectomy, and anti-TNFα treatment has been shown to preserve BMD in RA patients and in CIA in mice. Mice deficient in IL-6 do not develop ovariectomy-induced bone loss.

Oestrogen also influences the skeleton through the endocrine system, increasing the production of insulin-like growth factor 1 (IGF-1), which has anabolic effects on bone. We found that HRT for two years in RA patients resulted in increased levels of IGF-1. In osteoblasts, oestrogen has been shown to increase the expression of osteoprotegerin (OPG), BMP-6, transforming growth factor (TGF)-β and IGF-1, which results in osteoblast formation and increased osteoclast apoptosis. In osteoclasts, oestrogen directly decreases the secretion of lysosomal enzymes and...
downregulates the sensitivity to RANKL. Oestrogen also stimulates proliferation and differentiation of regulatory T cells, which have been shown to suppress osteoclast formation. Interestingly, oestrogen withdrawal in women is associated with increased osteocyte apoptosis. Osteocytes inhibit osteoclast activity through TGF-β and oestrogen enhances this function.

The SORM raloxifene is approved for the treatment of post-menopausal osteoporosis. It has been shown to influence the serum levels of bone turnover markers in women with post-menopausal osteoporosis. In addition, serum OPG levels were found to be higher in post-menopausal women after raloxifene treatment, and the RANKL/OPG ratio was decreased by raloxifene treatment of osteoblastic cells in vitro. Raloxifene also decreased osteocyte apoptosis both in vivo and in vitro. However, the effect of raloxifene in post-menopausal RA has not yet been evaluated.

**Treatment of Osteoporosis in Rheumatoid Arthritis**

Different therapies have been used in the management of osteoporosis in RA. Today, anti-osteoporosis therapies are divided into therapies that predominantly stimulate bone formation (parathyroid hormone and strontium ranelate) or inhibit bone resorption (bisphosphonates, strontium ranelate, HRT and SORM). In addition, bisphosphonates, oestrogen and SORM seem to inhibit osteocyte apoptosis. Both oestrogen deficiency and arthritic disease have deteriorating effects on bone density, and HRT was found to ameliorate arthritis in some studies, however, to also increase BMD. However, the use of HRT has decreased over the last few years due to the possibility of serious side effects. Bisphosphonates are often used in osteoporosis, and intermittent treatment with the bisphosphonate etidronate was found to increase BMD, as well as retarding the development of erosions in RA, but in another trial radiological outcome was not influenced.

Etidronate also increased BMD in steroid-treated patients with RA and polymyalgia rheumatica. Both alendronate and risedronate have been shown to increase BMD in RA patients on glucocorticoid therapy. Risedronate also reduced the risk of vertebral fractures in a large study of patients treated with corticosteroids and different diagnoses, including RA. Treatment with calcium and vitamin D increased BMD in the lumbar spine and trochanter in RA patients on long-term low-dose glucocorticosteroids. In post-menopausal women on HRT with corticosteroid-induced osteoporosis (~50% were RA patients), treatment with the anabolic agent parathyroid hormone (PTH) analogue improved BMD significantly more in the lumbar spine in women on HRT and PTH compared with those on HRT alone. New therapeutic compounds preventing both generalised bone loss and erosions in RA are under development. One example are substances that influence the RANKL/OPG/Greppor activator of NF-κB (RANK) system, thereby reducing osteoclast differentiation and activation. Recently, it was shown that a human monoclonal antibody to RANKL, denosumab, increased BMD in post-menopausal women. Denosumab is also an attractive candidate agent for inhibiting bone loss in arthritis. Raloxifene, which we found to have both antiarthritic and antosteoporotic effects in experimental post-menopausal arthritis in mice, also seems to be a promising treatment candidate in post-menopausal RA.

**Concluding Remarks**

Both oestrogen deficiency and inflammation promote the development of osteoporosis in post-menopausal RA. Some of the molecular pathways leading to increased osteoclast activity are similar after menopause and in inflammatory conditions. HRT has been shown to increase BMD in post-menopausal RA, while also decreasing disease activity and inflammation, but is no longer recommended for long-term therapy due to the risk of serious side effects. Based on our studies in mice, we suggest that selective modulation of ORs could provide a way of obtaining the positive bone effects of oestrogen therapy while avoiding the serious side effects. This needs to be studied further in post-menopausal RA.

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