New Approaches to the Diagnosis and Treatment of Postmenopausal Osteoporosis

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Introduction

The incidence of osteoporotic fractures in postmenopausal women is very high. In the US and UK, approximately 40-50% of all women will suffer at least one osteoporotic fracture during their lifetime (Table 1)[1]. Also in men, osteoporosis is prevalent. In USA, 13% of all men will suffer at least one of osteoporotic fracture, while in the UK this figure is about 20%. But the problem is about to increase even further since the proportion of senior citizens is increasing in many populations. In Denmark for example, the number of persons aged 65 years or more will increase by approximately 50% during the next 40 years.

Osteoporosis is defined as a disease of “decreased bone mass and deteriorated bone structure to such an extent that bone strength is decreased and the risk of fracture increased”[2]. Peak bone mass (the maximum bone mass attained during adolescent years) and post-menopausal as well as age-related bone loss are important concepts to understand the pathogenesis of this disease.

Genetic factors and osteoporosis

Twin and family studies have demonstrated that the peak bone mass is to a large extend genetically pro-

<table>
<thead>
<tr>
<th>Biological function</th>
<th>Gene</th>
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<tbody>
<tr>
<td>Hormone and other receptors</td>
<td>Vitamin-D receptor</td>
</tr>
<tr>
<td></td>
<td>Estrogen receptor</td>
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<tr>
<td></td>
<td>LDL receptor-related protein-5 (LRP5)</td>
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<tr>
<td>Growth factors and cytokines</td>
<td>Transforming growth factor-beta</td>
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<td></td>
<td>Sclerostin</td>
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<td>Osteoprotegerin (OPG)</td>
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<td>Bone matrix proteins</td>
<td>Collagen type-1-alpha-1</td>
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<td></td>
<td>Osteocalcin</td>
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<tr>
<td>Miscellaneous</td>
<td>Methyl tetrahydrofolate reductase (MTHFR)</td>
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</tbody>
</table>

Table 1. The incidence of osteoporotic fractures in persons age 50+ years in different countries (adapted from Johnell et al.[1])

<table>
<thead>
<tr>
<th>Country</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (%)</td>
<td>39.7</td>
<td>13.1</td>
</tr>
<tr>
<td>Australia (%)</td>
<td>42.1</td>
<td>-</td>
</tr>
<tr>
<td>Sweden (%)</td>
<td>46.4</td>
<td>22.4</td>
</tr>
<tr>
<td>United Kingdom (%)</td>
<td>53.2</td>
<td>20.7</td>
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Table 2. Some of the genes currently associated with low bone mass and/or increased risk of fracture (candidate genes)

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grammed. Genetic factors are estimated to account for 50-80% of the inter-individual variation in bone mineral density (BMD) in both women and men[3~5]. A growing list of candidate genes comprising genes encoding hormones and receptors, growth factors and cytokines, bone matrix proteins, and “other genes” are currently linked with bone mass or the risk of fractures (Table 2). One of these, the LDL receptor-related protein-5 (LRP5) gene is coding for membrane receptor that interacts with Wnt in activating the beta-catenin pathway, eventually leading to bone formation by osteoblasts. Loss-of-function mutation in LRP5 leads to the osteoporosis-pseudoglioma syndrome (OPPG) with multiple fractures and eye disease[6]. Conversely, gain of function mutation in LRP5 enhances Wnt signaling and leads to autosomal dominant osteopetrosis type-I also called “high bone mass phenotype”[7~9]. Thus, it is evident that mutations in the LRP-5 gene are important for some rare forms of osteoporosis. Common polymorphisms, however, in the same gene lead to subtle changes in the affinity to Wnt and is associated with BMD 2-3% lower than the wild type of this gene in women[10]. Recently, preliminary data have suggested a similar association in men[11]. Another example is the methylenetetrahydrofolate reductase (MTHFR) gene. Rare mutations in this gene lead to homocysteinuria and accompanied by osteoporosis. Frequent polymorphisms in the same gene, however, seem relevant to common post-menopausal osteoporosis. In the Danish Osteoporosis Prevention Study, we followed close to 1,000 untreated post-menopausal women for 5 years after the menopause. The relative risk of fractures in patients with the TT phenotype in the MTHFR gene was 2.4 fold increased compared with the background population[12] (Fig. 1). Recently, the same polymorphism has been linked to peak bone mass in men[13]. Based on our current knowledge, only rare cases of osteoporosis are monogenetic disorders. Interaction between many genes seems, however, to be part of the pathogenesis of the common forms of post-menopausal and age-related osteoporosis. Further understanding of these interactions may increase our ability to predict fracture risk and bone loss.

Post-menopausal decline in estrogen levels

Post-menopausal decline in estrogen levels has been associated with osteoporosis for several decades. Today, however, the molecular mechanisms responsible for this association have largely been unraveled as recently reviewed by Pfeilschifter[14] (Fig. 2). Osteoblasts express estrogen receptors and estrogen increases osteoblastic bone formation. Estrogen also increases osteoblastic production of BMP-2 (bone morphogenic protein) and TGF-beta (transforming growth factor beta) again leading to bone formation. Moreover, lymphocytes and marrow cells produce a number of inflammatory cytokines that increase bone resorption, i.e. IL-1, IL-6, TNF-alpha, and RANK-ligand. It is now evident that estrogen decreases lymphocyte and marrow cell production of these cytokines. Also, estrogen enhances osteoblastic production of OPG (osteoprotegerin) that decreases the effects of RANK-ligand on bone resorption. Finally, it’s been proposed that estrogen may act on the pituitary to increase ACTH release, increase cortisol slightly and thereby inhibit lymphocyte and marrow cell production of cytokines slightly. Thus, we have a firm handle on how loss of estrogen leads to osteoporosis.

Smoking and other life-style factors

An often neglected risk factor for osteoporosis is
smoking. Danish cohort-studies comprising more than 13,000 women and 17,000 men with a follow-up period of 5 to 32 years have demonstrated that smoking increases the risk of hip fracture 1.4-fold. Indeed, 19% of all hip fractures were attributable to smoking alone[15]. Most important, however, the risk of fractures were normalized after cessation of smoking after only 5 years[15,16]. Many other modifiable risk factors are important for the risk of osteoporosis and fractures. Vitamin-D is discussed below, while exercise, body weight, alcohol consumption, and medication (especially glucocorticoids) are beyond the scope of the present paper.

Pharmacological treatment of osteoporosis

Primary prevention is defined as efforts to increase bone mass or prevent fractures in the general population. Secondary and tertiary prevention are the treatment of patients with osteoporosis and manifested osteoporosis (i.e. prevalent fractures), respectively.

Vitamin-D

Mild vitamin-D deficiency and vitamin-D insufficiency are prevalent in many countries at high latitudes or in populations avoiding sun exposure (e.g. institutionalized elderly). Thus, approximately 80% of the elderly Danish population has low vitamin-D levels[17]. In a Danish population-based study, 9,605 individuals were randomized to receive 1000 mg of calcium and 400 units of vitamin-D every day for 36 months, a fall prevention program (i.e. a nurse visited the home and gave advice on preventive measures), both interventions, or no intervention. In the vitamin-D group, the incidence of all clinical fractures decreased by 18% during the 3 year follow-up period[17]. These data are backed up by a recent meta-analysis performed by Bischoff-Ferrari et al.[18]. This showed that treatment with 700 or 800 IU of vitamin-D per day was associated with a significant reduction in the risk of hip fractures and non-vertebral fractures amounting to 26% and 23%, respectively. In contrast, no positive effect was found in two studies applying smaller doses of vitamin-D (400 IU/day or less).

Estrogen and selective estrogen receptor modifiers

Women’s Health Initiative (WHI) study showed that estrogen decreases the risk of hip fractures by about 50%[19]. Similar data have been published on “all fractures”[20] and forearm fractures[21,22]. Long-term use of estrogen and estrogen-progesterone, however, increases the risk of thrombo-embolic complications and breast cancer. This precludes the long-term use of estrogen in women without climacteric symptoms and has decreased the use of these hormones in the prevention of osteoporosis[23]. Women, who need estrogen to alleviate climacteric symptoms may, however, now be reassured that this treatment prevents osteoporosis and informed on the magnitude of the risk of breast cancer, cardiovascular events, and thrombo-embolic complications. Fortunately, a number of other drugs are applicable and new drugs are
now coming to the market.

Raloxifene, a selective estrogen receptor modifier (SERM), acts on the estrogen receptor mimicking the effects of estrogen on bone while having antagonist effects on other tissues, for example the breast. In the MORE-trial[24], raloxifene treatment decreased the risk of fracture by about 50% in patients without any pre-existing vertebral fractures and slightly less in those patients who had prevalent vertebral fracture. SERMs are especially appealing since they have a number of non-skeletal effects as well. In a subgroup of patients with high cardiovascular risk participating in the MORE-trial, raloxifene resulted in a significant decrease in the number of cardiovascular events. Raloxifene also decreased the number of breast cancer cases. On the other hand, these drugs increase the risk of venous thrombo-embolism to the same extend as estrogen[25].

**Bisphosphonates**

Bisphosphonates are currently the most widely used anti-osteoporotic agents world-wide and numerous studies have demonstrated their ability to prevent bone loss. Etidronate[26,27], alendronate[28~31], risedronate[32,33], ibandronate[34], and pamidronate[35] have been demonstrated to decrease the occurrence of vertebral fractures by approximately 50%. In contrast, only alendronate and risedronate have been demonstrated to decrease the incidence of peripheral fractures.

Like estrogen, bisphosphonates are anti-catabolic drugs. Their main effect is to decrease both bone resorption and bone remodelling. This in turn reduces the remodeling space (i.e. the number of open resorption lacunae) and thus the number of stress risers in the trabecular network and this may be the most important effect regarding increasing bone strength. By slowing down bone turnover, bisphosphonates indirectly increases the mean age of the bone tissue, and increases the degree of mineralization. This leads to increased BMD and may probably explain some of the anti-fracture efficacy of these drugs.

**Parathyroid hormone–like drugs**

Recently, parathyroid hormone (PTH(1-34)) was approved for use in US and Europe. PTH(1-34) or teriparatide is synthesized by genetically modified E. Coli, and this drug has dramatic anabolic effects on bone mass. It increases BMD in the lumbar spine and hip by 9.7% and 2.6%, respectively, after 18 months. This translates into a pronounced risk reduction considering vertebral fractures (65%) and appendicular fractures (35%)[36]. In a randomized comparison of teriparatide and alendronate, BMD in the spine increased in the alendronate group during one and half year by about 4-5%. In contrast, a 10% increase was seen in the teriparatide group. This difference is even more pronounced in the trabecular bone within the vertebral bodies where alendronate increased BMD about 4 to 5% while teriparatide increased this parameter by almost 18%[37]. Teriparatide increases bone remodelling and may initially lead to an apparent decrease in bone mass due to decreased degree of mineralization and expansion of the remodelling space. With time, however, bone dimensions, cortical thickness, and the number of trabecular elements increase leading to increasing bone strength.

**Strontium ranelate**

Strontium ranelate is a new drug recently registered for clinical use in Europe. The organic part of the molecule (ranelic acid) is biologically inert but facilitates absorption and increases bioavailability of strontium. This drug seems to have both anabolic and anti-resorptive effects and constitutes a new class of “dual action bone agents”.

Strontium ranelate enhanced preosteoblastic cell replication and increased collagen synthesis by osteoblast[38]. Also, mature osteoblasts are stimulated to produce more non-collagenous protein as well as collagen. In different in vivo model systems, strontium ranelate has been demonstrated to decrease bone resorption[39].

Strontium ranelate has been tested in a comprehensive clinical program. The pivotal phase-III studies took places in 75 centers in 12 countries, including Denmark, and the compound is currently been tested in Korea and other Asian countries. During the “First study”, a run-in period of 2 weeks to 6 months, vitamin-D status was assessed and supplementation administered with both vitamin-D and calcium in order to overcome any deficiencies (Fig. 3). After this, 1649 patients with at least one vertebral fracture at baseline were included in the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial[40] and 5,091 patients with low BMD in the hip were included in the Treatment of Peripheral Osteoporosis (TROPOS) trial[41]. In both studies, participants were randomized to strontium ranelate (2 g/day) or placebo. The main analysis
was performed after 3 years, however, both studies continue for long-term follow-up. During the entire study period, all participants received calcium and vitamin-D supplementation in addition to the study drug or placebo.

In both SOTI and TROPOS, BMD of the lumbar spine increased significantly by 14% (Fig. 4). Strontium has a higher atomic number than calcium and thus attenuates X-rays more than calcium. As a consequence, approximately 50% of the increase in BMD may be due to the strontium content in the bone perse. Similarly, BMD of the femoral neck increased by 8% compared with placebo.

In clinical terms, treatment decreased the incidence of vertebral fractures by 49% during the first year of treatment and by 41% during the three year of treatment (Fig. 5). This corresponds to a "number-needed-to-treat" of only 9 to avert one vertebral fracture. Post-hoc analysis of the pooled data from SOTI and TROPOS demonstrated a risk reduction of 40% was found in clinical vertebral fractures. Also, a similar risk reduction was found in patients with and without prevalent fractures at baseline, in patients more than 80 years old, and in patients with osteopenia. Treatment also decreased the risk of peripheral fractures by 16% during the 3-year period in the intention-to-treat analysis; i.e. this analysis included all patients. In the per-protocol analysis (i.e. restricting the analysis to patients complying with the protocol) the effect was even more impressive - a 33% reduction in the risk of peripheral fractures. Strontium ranelate also decreased the risk of hip fractures in predefined high-risk group (i.e. patients above the age of 75 years and with a T-score ≤ -3) by 36% (Fig. 6).

It has been our experience throughout the studies and in...
the clinical setting that this drug is very well tolerated. The occurrence of nausea and diarrhea was slightly increased especially in the first part of treatment. A slight, but significant, increase in the occurrence of deep vein thrombosis was also seen. The absolute risk of this complication, however, was very low. At this point we have no biological explanation for this increase, but further analysis and data collection are carried out to resolve this.

Conclusion

Osteoporosis is highly prevalent and may increase substantially during the next years due to changes in demographics. A total of 45% of all women and 15% of all men are expected to suffer at least one osteoporotic fracture during the lifetime.

Pathogenesis of osteoporosis is well documented in a number of patients. We have a good handle on how post-menopausal decline in serum estrogen affects bone and we are beginning to understand, how different genes and polymorphisms affect bone mass.

Vitamin-D supplementation is important in many countries and in risk-groups (e.g. elderly and institutionalized persons). Also, preventive measures are important. Thus, approximately 16-19% of all hip fractures is be attributable to smoking.

A number of pharmacological therapies decrease the incidence of fractures. These drugs may be classified as anti-resorptive (calcium and vitamin-D, bisphosphonates and SERMs), or anabolic (PTH1-34). Finally, strontium ranelate is a new dual-action bone agent that reduces the incidence of both vertebral, peripheral fractures, and hip fractures (in the high-risk group) with very few side effects.

This leaves us with a new landscape of osteoporosis treatment where most patients can now be offered evidence-based treatment of osteoporosis.

Questions and answers:

**Question.** Are you sure that strontium ranelate stimulates osteoblast formation? You showed no data on the mechanism of action on the molecular level.

**Answer.** Data have shown that strontium interacts with calcium receptor and that this may be involved in the increase in bone formation seen in vitro. But, the exact molecular mechanisms of action are currently unknown. Further work clearly has to be done on that issue.

**Question.** What is the therapeutic window for strontium ranelate in osteoporosis?

**Answer.** The dose-finding study applied doses of 0.5, 1, and 2 grams/day. The most pronounced effect was found with the highest dosage and this was chosen for further development. In animal studies, very high doses may lead to osteomalacia, however, no cases of osteomalacia were seen in bone biopsies in the human studies.

**Question.** Do you use estrogen in the treatment of osteoporosis?

**Answer.** We still use estrogen in young (i.e. below the age of 50 years) post-menopausal women. In these women, we usually advise the use of estrogen until the
age of 50 years. In women aged 50 years or more, we are now reluctant to apply long-term treatment. The advice from the Danish Health Board is to keep treatment as short as possible (i.e. less than 3 years), to use the lowest possible dosage, and to interrupt treatment every 1-2 years to evaluate climacteric symptoms. Follow-up on the WHI study, however, have just reported that a significant number of the patients is back on estrogen after a period of interruption. This demonstrates that many women have severe climacteric symptoms and feel that the benefits of treatment outweigh the risks. We are now in the position to communicate the exact risk associated with such treatment and let the patients decide.

Question. You showed excellent data on strontium; BMD increased remarkably and fracture rate decreased. Do you think that strontium improves bone quality, and how does strontium ranelate compare with bisphosphonates in that respect?

Answer. Bisphosphonates act primarily by increasing mean age of bone and decreasing bone resorption and remodeling spaces (the number of open osteoclastic lacunae). They are, however, not anabolic. Strontium acts differently; it decreases bone resorption, but not to the same extend as bisphosphonates. Biopsy data show that strontium increases cortical thickness and also increases mineral appositional rate. So it seems that strontium has dual action; both anti-resorptive and anabolic effects. As to the idea of bone quality, this is difficult to assess. Hopefully, we will be able to do this in the future.

Reference

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