New hopes in the treatment of osteoporosis in men

Recent discoveries of several new extracellular molecules have advanced our knowledge of osteoblast–osteoclast interaction and make them a promising target for developing new agents for managing osteoporosis.

In the last few years, osteoporosis in men has been recognized as an important public health problem. Not only do one-third of all hip fractures occur in men, but mortality rates in men with osteoporotic fractures are usually higher than in women [1]. The pathophysiology of idiopathic osteoporosis in men is rather complex. The traditional view emphasizes the role of testosterone, the major male sex hormone, in the regulation of bone metabolism. Nevertheless, reports of osteoporosis in men with aromatase deficiency [2] or estrogen-receptor (ER) gene [3] mutations raise the possibility that androgens’ anabolic action on bone is mainly mediated by the aromatization of testosterone to estrogen. Indeed, a number of studies revealed that bone mineral density (BMD) in elderly men is more closely related to estrogen than to testosterone levels [4,5].

In contrast to women, for whom several large, controlled and prospective trials have proved the efficacy of antiresorptive and anabolic drugs in reducing fracture-risk [6–9], only a small number of trials, with limited sample size, have been performed for men [10–13]. Initially, pharmacotherapy for osteoporosis has mainly been directed towards the suppression of bone resorption, although agents that stimulate bone formation have recently become available. Bisphosphonates and parathyroid hormone (PTH) have generally been accepted for use in men with osteoporosis, while the impact of androgen therapy is less clear.

Bisphosphonates have been proposed as the first choice for the treatment of osteoporosis in men, with results of clinical trials demonstrating significantly increased BMD at the lumbar spine and femoral neck [10] and reduced vertebral fracture risk [11]. These agents bind to the bone mineral surface, leading to the inactivation and programmed death of osteoclasts. However, a recent report of nine patients (eight postmenopausal women and one man) who sustained spontaneous nonvertebral fractures due to severe suppression of bone remodeling while on alendronate therapy [12] raises concern about their prolonged use. Unlike the bisphosphonates, PTH is an anabolic agent that stimulates bone formation. Intermittent administration of low-dose PTH in postmenopausal women demonstrated a 65% reduction in the rate of vertebral fractures and a 53% reduction in nonvertebral fractures [9]. In randomized clinical trials in men with idiopathic osteoporosis, daily subcutaneous injection of PTH significantly increased lumbar spine and femoral neck BMD compared with placebo [13,14]. A recent study also revealed that previous treatment with bisphosphonates might attenuate PTH-induced stimulation of bone formation [15].

The increasing body of knowledge concerning osteoporosis opens the door to new agents in the treatment of osteoporosis in men, primarily, selective ER modulators (SERMs) and selective androgen-receptor modulators (SARMs). Elderly men experience an age-related decline in serum testosterone, leading to hypogonadism, known as androgen decline in aging males or andropause. This decreased testosterone level is associated with an increased risk of osteoporosis and low trauma fractures. Androgen-replacement therapy in hypogonadal men decreases bone resorption, stimulates bone formation [16] and, subsequently, increases lumbar spine and femoral trochanter BMD [17]. Again, androgen use in eugonadal men, who represent the majority of men with osteoporosis, remains controversial [18,19]. Early studies revealed beneficial effects of testosterone treatment on BMD [19]. However, there is a great concern about the long-term safety regarding the risk of prostate disease. In this respect, the development of SARMs could become a great advance in the treatment of osteoporosis in men. To be suitable for usage, these drugs should have a desirable efficacy profile in muscle, bone and sexual function, but without the common side effects associated with androgen use. However, a few of the SARMs recently described exhibit a weak separation...
between their effects on prostate and bone [20,21]. Still, in a recent study on rodent models, a highly selective androgen-receptor ligand, LGD2226, was shown to inhibit resorption rate in cancellous bone and enhance formation in cortical bone, resulting in an overall increase in bone strength [22]. On the other hand, compared with testosterone, prostate growth was considerably reduced in LGD2226-treated animals [22].

Although testosterone is capable of directly affecting bone metabolism through specific androgen receptors on bone cells, as has already been mentioned, most of its skeletal effects are mediated by aromatization to estradiol. It has been reported that estrogen may also influence the acquisition of peak bone mass in men [23]. In a certain way, this is supported by preliminary data of the Genetics Of Osteoporosis Study, which show the association of peak bone mass with microsatellite TA dinucleotide repeat polymorphism within the ER-α gene [Unpublished Data].

Although estrogen acts through two distinctive receptors, ER-α and -β, ER-α appears to be the primary mediator of its actions on bone [24]. SERMs bind to ERs and, in much the same way that SARMs alter the conformation of the androgen receptor, produce 3D conformational changes resulting in differential gene expression. Although SERMs (raloxifene) have been approved for the treatment of osteoporosis in postmenopausal women, we have recently proposed that it could also be useful for the treatment of osteoporosis in elderly men [25]. SERMs exhibit an estrogenic effect in bone via binding with ER-α and -β on human osteoclasts and osteoblasts, but without the feminizing effect. Another SERM, lasofoxifene, has been demonstrated to inhibit bone turnover and prevent bone loss in orchidectomized adult male rats [26]. Raloxifene treatment in men receiving androgen-deprivation therapy for prostate cancer increases hip BMD in amounts comparable to that seen in postmenopausal women [27]. However, important questions regarding antifracture efficacy, dose regimen and side effects must be resolved before SERMs and SARMs can be safely and effectively used in the treatment of osteoporosis in men.

New studies targeting other molecules involved in the pathogenetic mechanism of osteoporosis, such as receptor activator of nuclear factor-κB (RANK), dickkopf (DKK), sclerostin and cathepsin K, offer us new hope in the management of osteoporosis. The recent discoveries of osteoprotegerin (OPG), RANK and RANK-ligand (RANKL) rapidly expanded the understanding of bone remodeling. RANKL is an osteoblast-derived factor that binds to RANK, a receptor found on mature osteoclasts and their precursors, stimulating osteoclast differentiation and activation [28]. OPG, a member of the tumor necrosis factor (TNF)-α receptor family, prevents RANKL from binding to RANK and decreases osteoclast numbers [29]. Therefore, pharmacological intervention with recombinant OPG or RANKL antibody is promising as a potential treatment for osteoporosis. Preclinical studies demonstrating the skeletal benefits of RANKL inhibitors support this rationale [30,31]. A recent study has demonstrated reduced bone loss associated with inflammation in mice treated with OPG and TNF-α antibody [32]. However, the definitive answer regarding the potential use of RANKL inhibitors in osteoporosis management will be yielded by a randomized clinical trial investigating the antifracture efficacy of a fully human monoclonal antibody against RANKL, known as denosumab, which is currently ongoing.

‘...data suggest that future therapy for osteoporosis could aim at blocking the action of DKK1 and sclerostin.’

The molecular mechanisms that regulate osteoblast development include several factors that could modify osteoblast differentiation and apoptosis. Signaling pathways critical for osteoblast differentiation and function involve both the Wnt and bone morphogenetic protein (BMP) pathways. Wnt signaling is important in the response to mechanical loading [33], and can also affect peak bone mass [34]. BMPs enhance osteoblast differentiation and bone formation via specific BMP type I and II receptors and their transcription effector proteins, termed Smads. There are a number of molecules that are capable of interacting with Wnt and BMP signaling. One of these, DKK homolog 1, has been shown to inhibit the Wnt pathway via binding and sequestering cofactors in Wnt ligand-mediated signaling, such as the low-density lipoprotein receptor-related proteins 5 and 6 [35,36]. High concentrations of DKK1 found in the bone marrow of patients with multiple myeloma may, by inhibiting Wnt signaling, contribute to the reduced rate of bone formation and osteolytic lesions that are characteristic of this malignancy [37]. Conversely, it has been proposed that an opposite response occurs in malignancies where decreased DKK1 results in osteoblastic metastases [38]. In favor of this hypothesis, DKK1-neutralizing antibody has
been demonstrated to increase osteoblast numbers, reduce osteoclast numbers and stimulate new bone formation in multiple myeloma [39]. Similarly to DKK1, sclerostin also has an inhibitory effect on bone formation by inhibiting osteoblast development [40] and stimulating osteoclast apoptosis [41]. Sclerostin is secreted by osteocytes, the most abundant cells in bone, functioning as a BMP-pathway inhibitor [40]. Mutation of the gene encoding sclerostin (SOST), resulted in sclerosteosis, a rare disease characterized by progressive bone thickening and generalized osteosclerosis [42]. Van Buchem disease, another bone dysplasia with the same characteristics, is caused by 52 Kb deletion 35 Kb downstream of the SOST gene [43]. Finally, it has been shown that treatment of mice with sclerostin-blocking antibody increased BMD [44]. All of these data suggest that future therapy for osteoporosis could aim at blocking the action of DKK1 and sclerostin.

Cathepsin K is a cysteine protease which is abundantly expressed in human osteoclasts [45]. Recent reports of osteopetrosis in cathepsin K knockout mice strongly suggest that this molecule has an important role in osteoclast-mediated bone resorption [46]. Moreover, the finding in cynomolgus monkey that inhibition of cathepsin K resulted in a reduction in the rate of bone resorption also reveal it to be a potential new approach in osteoporosis treatment [47].

In conclusion, bisphosphonates and PTH are currently the most efficacious therapy available for men with osteoporosis. Conversely, the efficacy and safety of SERMs and SARMs remains to be tested in randomized clinical trials. However, recent discoveries of several new extracellular molecules have advanced our knowledge of the osteoblast–osteoclast interaction and make them a promising target for developing new agents for managing osteoporosis.

Bibliography

11. Morrisey EG, Song X, Kelly JJ: Parathyroid hormone improves bone formation in multiple myeloma [39]. Similarly, inhibition of cathepsin K resulted in a reduction in the rate of bone resorption also reveal it to be a potential new approach in osteoporosis treatment [47].
Results of selective androgen-receptor modulators in rodent models.


