Is there potential for strontium ranelate in the management of osteoarthritis?

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Practice Points

- Osteoarthritis (OA) is the most common joint disorder in the world. In the western population, it is one of the most frequent causes of pain, loss of function and disability in adults.

- Whereas several medications have shown their ability to improve symptoms in OA, none of them is unequivocally accepted worldwide for structure modification.

- Strontium ranelate (SR) is a drug currently marketed for the management of postmenopausal osteoporosis and osteoporosis in men, and has been demonstrated to reduce fractures at all major sites in osteopenic and osteoporotic patients, independently of the severity of the disease and the age of the patients.

- In cellular and molecular models of OA, SR prevents subchondral bone resorption and stimulates cartilage matrix synthesis.

- SR reduces the progression of in vivo experimental dog OA by inhibiting expression of mediators of cartilage degradation and reducing bone sclerosis.

- In women treated with SR for postmenopausal osteoporosis, biological markers of bone and cartilage degradation are significantly reduced and progression of spinal OA is decreased.

SUMMARY Although the exact process of osteoarthritis (OA) has yet to be elucidated, increasing evidence suggests that intensive biological and mechanical cross-talk between subchondral bone and cartilage becomes abnormal in OA. Compounds with a potential to influence the cartilage–subchondral bone unit, based on their mechanical or biologic properties might constitute a breakthrough in medical treatment of OA. Strontium ranelate (SR)
Osteoarthritis (OA) is a complex disease entity that is difficult to diagnose and define. It is thought to be the most prevalent chronic joint disease. Pain and loss of function are the main clinical features that lead to treatment [1]. All tissues of the joint are involved, although the loss of articular cartilage and changes in adjacent bone remain the most striking features [2]. Although the exact process of OA has yet to be elucidated, increasing evidence suggests that intensive biological and mechanical cross-talk between subchondral bone and cartilage becomes abnormal in OA [3]. For many years, treatment of OA focused on the reduction of pain and stiffness, and on the maintenance and improvement of functional capacities. Recent innovations in the pharmaceutical drug-discovery environment have generated new clinical entities with the potential to become disease-modifying drugs for OA. Whereas regulatory agencies acknowledge that such compounds may be granted a disease-modifying indication, providing they demonstrate that intensive biological and mechanical cross-talk between subchondral bone and cartilage becomes abnormal in OA [3]. For many years, treatment of OA focused on the reduction of pain and stiffness, and on the maintenance and improvement of functional capacities. Recent innovations in the pharmaceutical drug-discovery environment have generated new clinical entities with the potential to become disease-modifying drugs for OA. Whereas regulatory agencies acknowledge that such compounds may be granted a disease-modifying indication, providing they demonstrate that intensive biological and mechanical cross-talk between subchondral bone and cartilage becomes abnormal in OA [3].

Strontium ranelate (SR) is an antosteoporotic drug acting on bone remodeling based on the concept of inducing opposite effects on bone resorption and formation. Preclinical studies showed that this dual effect results in increased bone mass and improved bone microarchitecture and strength in intact rodents, and in prevention of bone loss in osteopenic animals [6].

Numerous pharmacological studies showed that SR activates multiple signaling pathways in bone cells to achieve its pharmacological actions. Notably, activation of the calcium-sensing receptor by strontium in osteoclasts and osteoblasts leads to activation of phospholipase Cβ, inositol 1,4,5-triphosphate, release of intracellular Ca²⁺, and activation of MAPK ERK 1/2 and Wnt/NFATc signaling. Strontium-mediated activation of these pathways results in the modulation of molecules such as the receptor activator of NF-κB (RANKL) and osteoprotegerin that regulate bone resorption, and the regulation of genes promoting osteoblastic cell replication, differentiation and survival [7].

To evaluate the efficacy of SR in preventing vertebral fractures, 1649 postmenopausal women with osteoporosis (low bone mineral density) and at least one vertebral fracture were randomized to SR (2 g/day) or placebo for 3 years. New vertebral fractures occurred in fewer patients in the SR group than in the placebo group, with a risk reduction of 49% in the first year of treatment and 41% during the 3-year study period [8].

SR was also studied to assess its efficacy and safety in preventing nonvertebral fractures. SR
(2 g/day) or placebo were randomly allocated to 5091 postmenopausal women with osteoporosis in a double-blind, placebo-controlled, 5-year study with the main statistical analyses after 3 years of treatment. After 3 years, in the entire sample, relative risk (RR) was reduced by 16% for all nonvertebral fractures and by 19% for major fragility fractures in SR-treated patients in comparison with the placebo group. Among women at high risk of hip fracture (aged ≥74 years and low femoral neck bone mineral density), the RR reduction for hip fracture was 36% [9]. After 5 years, the fracture reduction for hip fracture was 43% [10]. Long-term treatment with SR was associated with sustained increases in bone mineral density over 10 years, with a good safety profile. The incidence of vertebral and nonvertebral fractures with SR in the population followed for 10 years was significantly lower than the incidence observed in a FRAX® (WHO, Geneva, Switzerland)-matched placebo group. RR reductions for vertebral and nonvertebral fractures were 35 and 38%, respectively [11].

Interestingly, the efficacy of SR on vertebral and nonvertebral fracture reduction was not dependent of the main determinants of fracture risk (i.e., age, baseline bone mineral density, prevalent fractures, family history of osteoporosis, baseline BMI and addiction to smoking) [12], neither was it modified by the level of fracture risk assessed by FRAX, a WHO-developed algorithm providing, on an individual basis, the 10-year probability of a major osteoporotic fracture (clinical spine, forearm, humerus or hip fracture) and the 10-year probability of hip fracture [13].

In a male population at risk of fractures, a marked increase in the mean lumbar, femoral neck and total hip bone mineral density was also observed with SR. A trend towards a lower incidence of fracture with SR was also observed [14].

Long-term exposure of postmenopausal women and elderly men to SR (up to 10 years) was associated with an overall satisfactory safety profile. A modest but significant increase in the risk of thromboembolic events was reported (i.e., an increase in RR, which was fourfold smaller than with estrogens or selective estrogen receptor modulators), mainly seen in patients with previous history or risk factors for deep venous thrombosis. Very rare severe cutaneous reactions were also reported but remained in the frequency range of dermatological side effects reported with other antiosteoporotic medications [15–17].

The EMA critically reassessed in the summer of 2012, the long-term risk/safety benefit of SR in osteoporosis and came to the conclusion that this ratio was still highly beneficial. However, the agency recommended that SR is not used in patients with a previous history of or major risk factors (e.g., immobilization) for deep venous thrombosis.

Previous reviews of the literature, reporting clinical and nonclinical actions of SR in cellular and animal models, as well as in postmenopausal osteoporotic women, suggested that this compound might also have some activity in OA [18].

Cellular & molecular effects of SR in OA
As previously mentioned, subchondral bone remodeling may be considered a primary attribute of OA and may be responsible for cartilage damage [19]. Moreover, it is believed that changes in OA subchondral bone consist of phases of bone resorption and of abnormal bone sclerosis [20]. Bone resorption is suggested to occur, at least in part, through the increased level of two proteolytic enzymes, matrix metalloproteinase (MMP)-2 and MMP-9, and RANKL, which are mainly produced by osteoblasts. SR modulatory effects on the above key factors were investigated in human OA subchondral bone osteoblasts. In OA cells, the expression levels of MMP-2 and MMP-9 were significantly decreased by SR. In OA cells, the expression and synthesis of osteoprotegerin was increased with SR. SR also significantly reduced the level of membranous RANKL. The authors conclude that these results provide new insights into the mode of action of SR on the metabolism of human OA subchondral bone osteoblasts and suggest that SR may exert a positive effect on OA pathophysiology by inhibiting, in these cells, the synthesis of key factors leading to bone resorption, a feature associated with the OA process [20]. These findings, however, might be specifically relevant to different phenotypes of the disease (i.e., adaptive or end-stage subgroups of OA). Whether SR might be more active in one subgroup or another remains to be elucidated.

These results are particularly interesting in the perspective of recent studies, which revealed that severity of OA is associated with increased levels of RANKL [21]. The important role of RANKL...
in OA is evidenced by the inhibitory effect of osteoprotegerin (a decoy receptor of RANKL) on IL-1-mediated OA [20,21].

SR was also shown to significantly increase serum IGF-1 levels in osteoporotic postmenopausal women [22]. IGF-1 is a potent inhibitor of IL-1β-mediated activation of NF-κB and apoptosis in chondrocytes [23]. IGF-1 is also responsible for upregulation of the COL2A1 gene, hence increasing type II collagen synthesis by a transcriptional control mechanism [24]. These results are in accordance with the previous demonstration that, in human chondrocytes, SR strongly stimulated proteoglycans production through an ionic effect of strontium, independent of the organic moiety. SR increased the stimulatory effects of IGF-1 on proteoglycan synthesis without stimulating the chondral resorption process assessed by stromelysin activity [25].

**Effects of SR in animal models of OA**

In dogs undergoing sectioning of the anterior cruciate ligament of the knee, oral administration of SR for 12 weeks generated strontium blood exposures within the clinical therapeutic range of OA patients treated with 1 or 2 g/day of SR. Strontium concentrations in synovial fluid correlated with strontium blood concentrations. SR treatment significantly reduced the progression of OA cartilage lesions and preserved the collagen network. The thickening of the subchondral plate found in the OA placebo-treated dogs was reduced by SR treatment. This observation may, however, look paradoxical, taking into account the bone-forming action of SR observed in osteoporosis. The increased gene expression levels of MMP-1, MMP-13, thrombospondin motifs 5 (ADAMTS5) and cartilage K found in OA cartilage were all reduced by SR treatment. A significant suppression of the increased levels of IL-1β in OA synovium by SR was also found. The authors concluded that this study was the first to demonstrate that SR reduces the progression of OA structural changes (both cartilage lesions and subchondral bone sclerosis) in an *in vivo* animal model [26,27]. It should however, be kept in mind that this canine study had a prevention set-up (direct treatment after OA induction) instead of an actual treatment set-up.

These observations can be put in parallel with the demonstration that alendronate, a bisphosphonate used for the management of osteoporosis, inhibits osteophyte formation in the rat model of post-traumatic OA [28].

**Effects of SR on biological markers of cartilage degradation**

In a subgroup of 2617 postmenopausal osteoporotic women who were originally included in a study assessing the effects of SR on nonvertebral fractures [9], the levels of C-telopeptide of type II collagen (CTX-II), corrected for urinary creatinine, were assessed at regular intervals for 3 years. There was a statistically significant difference between SR and placebo. This difference in the response of CTX-II appeared soon after 3 months, with the SR-treated subjects having approximately 15–20% lower values than placebo-treated subjects for the remaining study period [29]. In a subsequent analysis of the same study, CTX-II was significantly elevated at baseline in subjects with a history of OA compared with subjects who did not. SR caused a significant decrease from baseline in CTX-II over a 12-month period whatever the OA status. SR-treated patients had a significant decrease in CTX-II compared with placebo in both patients with or without a history of OA for up to 12 months, the difference still remained significant at 36 months in patients who did not have a history of OA. The authors concluded that this profile of changes over 3 years may reflect efficacy of SR against cartilage degradation, with an enhanced beneficial effect in subjects with early or mild clinical OA, with SR probably exerting its putative chondroprotective influence in early stages of the disease [30]. However, it should be noted that, for many authors, CTX-II is no longer considered an exclusive marker of cartilage damage, since it appears to be also released from bone [31].

In the past, some discrepancies have been observed between the effect of drugs tested for their structure-modifying effect in OA, on biological markers and on joint space narrowing. For instance, risedronate, a bisphosphonate licensed for the management of osteoporosis, decreased biological markers of cartilage degradation but did not decrease symptoms or slow radiographic progression in patients with OA of the medial compartment of the knee [32]. Whereas in that particular study, the failure to show an effect of risedronate was most likely related to weaknesses in the design of the trial (i.e., selection of patients with suboptimal joint space width at baseline), this may call into question the assessment of a
Effects of SR on spinal OA assessed in women with postmenopausal osteoporosis

A post-hoc analysis of pooled data from the studies assessing the effect of SR on vertebral [8] and nonvertebral [9] fractures was performed on 1105 women with osteoporosis and concomitant radiologic spinal OA at baseline, and for whom lumbar x-rays were available at baseline and over the 3-year treatment period. SR was investigated, over 3 years, for its potential effect to delay the progression of spinal OA.

The presence and severity of osteophytes, disc space narrowing and sclerosis in the lumbar intervertebral spaces was graded according to the method of Lane et al. [33], and an overall OA score was calculated for each intervertebral space. Back pain and health-related quality of life were assessed at baseline and after 3 years. The proportion of patients with a worsening overall spinal OA score was reduced by 42% in the SR group compared with placebo. Significantly more patients in the SR group experienced an improvement in back pain after 3 years compared with placebo, while no significant difference was observed in terms of health-related quality of life between these patient groups. The authors concluded from this post-hoc analysis that SR could reduce the progression of the radiographic features of spinal OA and back pain in women with osteoporosis and prevalent spinal OA [34].

The post-hoc nature of this observation, otherwise acknowledged by the authors, is a limitation of the study, hence the request for caution in the clinical transposition of the results.

Conclusion

In conclusion, whereas SR was originally developed as an antosteoporosis treatment, there is a convergent body of evidence for an effect in OA, including cellular and molecular effects on subchondral bone resorption and sclerosis, as well as on cartilage matrix production, supported by an in vivo decrease of cartilage degradation in dogs. These preclinical effects translate in human subjects into a reduction in biological markers of bone and cartilage degradation and in prevention of the progression of spinal OA, hence granting SR a putative role in the management of clinical OA.

To support this potential beneficial symptom and structure-modifying effect on OA, a double-blind, placebo-controlled trial, included more than 1600 ambulatory Caucasian men and women aged 50 years and over with primary knee OA of the medial tibio-femoral compartment and knee pain. Patients were randomly allocated to three groups (SR 1 g/day, SR 2 g/day or placebo). The primary end point of this trial is radiographic changes in joint space width from baseline in each group versus placebo. The main clinical secondary end point is the Western Ontario and MacMaster Universities Index at the knee [35,36]. The results of this study were recently published and showed that SR, at the dose of 1 and 2 g/day significantly reduced joint space narrowing at the medial tibio-femoral compartment of the knee, while only the dose of 2 g/day provided significant benefits, on pain and function in patients with primary knee OA [37,38].

Future perspective

OA is the most prevalent chronic joint disease, resulting in pain and loss of function in more than half of the elderly population. For many years, the management of OA concentrated on the relief of symptoms. Recent innovations in the pharmaceutical drug-discovery environment have generated new chemical entities with the potential to become disease-modifying drugs for OA. Whereas regulatory agencies acknowledge that such compounds may be granted a disease-modifying marketing authorization, providing they demonstrate that they can slow down disease progression and improve symptoms, none of them is unanimously accepted worldwide as the standard for preventing OA structural progression. Interesting results were published with nutriceuticals, including glucosamine sulfate (but not glucosamine hydrochloride) and chondroitin sulfate. The results of these trials were challenged, mainly because, in many parts of the world, these compounds are only available as over-the-counter formulations, which cannot be compared with the licensed drugs available in Europe [5]. Numerous research efforts have been recently put into understanding the mechanical and biological link between cartilage and subchondral bone in OA [19]. This better understanding of the cartilage–subchondral bone unit provides a basis for establishing
Exhaustive review of the molecular Determinant contribution revisiting the First paper demonstrating that an
reasonable expectations for the patient and providing medications, acting both on cartilage and on subchondral bone. The association between subchondral bone remodeling and clinical improvement in OA was recently supported by the demonstration that, in patients with advanced post-traumatic ankle OA, joint distraction for 3 month resulted in a decrease in pain and functional deficit, which was best correlated with disappearance of low-density areas in the subchondral bone [37]. SR, a drug marketed for the management of osteoporosis that has been shown to uncouple bone formation from bone resorption, appears to have beneficial effects on subchondral bone and on chondrocytes [19,20,25,27]. A large development plan for this molecule in OA has now been set up, based on robust preclinical, molecular, cellular and animal evidence. This was also supported by interesting preliminary human results, mainly obtained in postmenopausal women with OA. The future of OA management is most likely dependent upon molecules presenting a wide spectrum of activities, targeting different components of the joint.

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- of interest
- of considerable interest

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Is there potential for strontium ranelate in the management of osteoarthritis? | Review


First demonstration that strontium ranelate acts not only on chondrocytes but also on subchondral bone, using the most up-to-date methodology.


Interestingly demonstrating that strontium ranelate reduces progression of spinal osteoarthritis in postmenopausal women with osteoarthritis, based on a validated methodology.


First study to demonstrate the ability of an antiosteoporosis medication to improve symptoms and reduce the structural progression of osteoarthritis.