10.1515/chilat-2017-0004

PROBLEM-SOLVING ARTICLE

Does Local Application of Strontium Increase Osteogenesis and Biomaterial Osteointegration in Osteoporotic and Other Bone Tissue Conditions: Review of Literature

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Summary
Osteoporosis and other pathological bone conditions can impair bone regeneration properties, consuming in increased morbidity and decreased quality of life. Changes of bone healing can result in poor osteointegration and surgical failures if implants are used. To overcome and facilitate bone regeneration, more attempts are made to develop an ideal synthetic scaffold with better biocompatibility, osteoconductivity, bioactivity, osteoinductivity and interconnected porosity. It is considered that strontium, being similar to calcium, can be incorporated into the mineral phase of the bone remodeling. This quality had led strontium to be used as an osteoporotic medication to improve quality of bone and to reduce the risk of bone fractures. Also local application of strontium has been widely used within different biomaterials in tissue engineering researches.
In this review authors wanted to provide an overview about strontium, its mechanisms of action in bone tissue and initiated changes of bone remodeling within biomaterials.
Key words: osteoporosis, strontium, biomaterial, osteogenesis, osteointegration, bone

INTRODUCTION

Bone regeneration, provided by osteoblasts and osteoclasts, is influenced by complicated cross talk between the immune and skeletal systems, being regulated by many molecules like cytokines, growth factors, different receptors and transcriptional factors (46). When physiological process of bone metabolism is disrupted, weather by the disease or for experimental purposes, disbalance of normal bone turnover occurs. Osteoporosis being one of the most common musculoskeletal bone pathologies is characterized as a chronic age related disease with compromised bone strength (49). It affects one in three women and one in five men worldwide and can present with low energy trauma induced skeletal fractures leading to morbidity and changes in quality of life (45).

Strontium (Sr) is an alkaline earth metal with an atomic number 38 (31). Sr can be incorporated into the mineral phase of the bone remodeling due to the similarity to calcium ions (1). Strontium has shown dual action properties – it increases bone formation and decreases bone resorption, leading to a new bone formation, improved quality of bone micro architecture and strength (21). Thereby, strontium ranelate (SR) as anti-osteoporotic medication was first registered in Europe in 2004 and was indicated for women with postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures (43). Effectiveness of SR to prevent osteoporosis and reduce the risk of fractures is well demonstrated in large clinical trials (42), like The SOTI *(Spinal Osteoporosis Therapeutic Intervention*) trial, where SR increased bone mineral density, improved quality of life and reduced the risk of vertebral fractures by 33% (28) and the TROPOS (*Treatment of Peripheral Osteoporosis*) trial, where the risk of vertebral fractures was reduced by 43% but nonvertebral and hip fractures by 15% and 24% respectively (41). Moreover, SEKOIA (Strontium Ranelate Efficacy in Knee Osteoarthritis Trial) trial showed that administration of SR for 2g/day over 3 years is associated with a significant improvement in pain, physical activities and stiffness. Reduction of cartilage volume loss and bone marrow lesions were found on MRI in participants of SEKOIA trial (35). Unfortunately, systematic treatment with SR is associated with some adverse effects including headache, diarrhea, nausea and, rarely, cutaneous hypersensitivity (42). There is still ongoing discussion whether it increases life threatening cardiac events and venous thrombosis (6, 12).

The recognition of positive effects of strontium on bone tissue in different *in vitro* and *in vivo* studies, has led to its local application in variety of biomaterials, used in tissue engineering for better bone repair and regeneration (51). Long term local and targeted release of Sr ions from biomaterial or implant to surrounding bone tissue interface is considered as a good option to increase osseointegration of implant and to avoid adverse effects due to the oral administration of Sr (26).

Strontium

Strontium is an alkaline earth metal with an atomic number 38 and is mostly found in ocean water, nutritional supplements and food, like grains or seafood. Very small amount of Sr is up-taken through skin and lungs (31). In our body 99% of total amount of Sr is incorporated in the structure of new trabecular bone, close together connected to bone native hydroxyapatite (11). These features have led strontium attractive for medical applications. The similarity between Sr and calcium enables Sr to be incorporated into the mineral phase of the bone (1). It is calculated, that the amount of Sr in new compact bone is 3-4 folds higher than in old compact bone and 2-3 folds higher in new cancellous bone than in old one (27) due to higher bone turnover in cancellous than cortical bone (54). However, the total amount of Sr is noticeably smaller than calcium and reaches only 3.5% of the content of calcium found in our body (5).

Strontium ion interaction on bone cells

The role of strontium in bone mineralization and remodeling is increasing and new insights of morphopathogenetical mechanisms are found. Multiple intracellular signaling pathways are involved in strontium interaction on bone forming cells through different activated molecules, which promote their survival, proliferation and differentiation (51). It promotes an increase of formation of the mineralized matrix in osteoblast cell cultures, which are similar to the composition of native bone tissue (39).

Strontium and osteoblasts

During the treatment of strontium, multiple osteogenic genes can be prepossessed. For example, Runx2 (Runt-related transcriptional factor 2) is up-regulated through Sr ability to activate MAPK (mitogen activated protein kinase) phosphorylation in osteoblasts, initiating osteogenic differentiation (36). Due to the similarity between strontium and calcium ions, Sr can act on osteoblasts through the calcium sensing receptors (CaSR), activating cell replication via MAPK signaling, (37) Another Sr induced pathway through CaSR is activating ERK1/2 (extracellular signal related kinase) signaling pathways and osteoblast replication. Importantly, it was found that Sr activates Akt (protein kinase) pathway, mediating anti-apoptotic effect on osteoblasts (16). One more positive effect of Sr have been found by Rybchyn et al., where Sr decreased the expression of sclerostin, an inhibitor of the canonical Wnt (wingless-related integration site) signaling pathway, promoting β-catenin translocation into the nucleus of human osteoblasts and promoting osteogenesis (47). Others have found that Sr induces osteoblastic cell replication and differentiation via activating NFATc1 mediated canonical and non-canonical Wnt signaling pathways. NFATc1 (nuclear factor of activated T cells) are important transcription factor which regulates targeted genes in bone, increasing osteoblast replication and functions (15). Sr also enhances the release of different signaling molecules involved in regulation of bone turnover by mechanically stimulated osteocytes (3). In vitro study by Caverzasio et al., showed another mechanism of Sr and indicated that Sr can activate the FGF/FGFR (fibroblast growth factor receptor) pathway enhancing osteoblast growth (7).

Strontium and osteoclasts

Furthermore, strontium has positive effect on bone remodeling by inhibiting osteoclastogenesis and bone resorption (4). Sr stimulates expression of osteoprotegerin (OPG), a member of tumor necrosis factor superfamily, which plays important role in the regulation of bone metabolism through OPG/RANK/RANKL mechanism, decreasing the expression of RANKL (receptor activated nuclear factor kappa ligand) thus inhibiting osteoclast differentiation and function (2). Bakker et al., found that Sr can also affect mature osteoclasts and induce their apoptosis through calcium sensing receptors (3).

Strontium and adipocytes

Adipogenesis also plays an important role in pathogenesis and progress of osteoporosis. Strontium has shown the ability to inhibit differentiation of adipocytes from bone marrow mesenchymal stem cells and increase osteoblast differentiation (24). This is because of strontium ability to inhibit PPARγ2 (peroxisome proliferator activated receptor gamma2) adipocyte transcription factor and decreasing replication of adipocyte (10, 48).

Strontium and biomaterials

Many studies have been investigating Sr effects in different biomaterials and results are encouraging. Strontium ions are being incorporated in different biomaterials and metallic implants like synthetic hydroxyapatites, glass ceramics, bioactive glasses, calcium phosphate cements or metallic implants with different alloys, searching for increased bone quality and formation in bone tissue defects or around osseointegrating implants (22, 25, 29, 33, 52). In recent years there is a development of injectable materials for filling bone defects as minimally invasive techniques. Also strontium rich injectable hybrid systems have been developed with promising results in tissue engineering (29). An ideal bone substitutive scaffold should induce and restore biological functions of bone matrix, where cells and growth factors are needed, but also have the right properties with respect to degradation, cell binding, cellular uptake, non-immunogenicity, strength and flexibility (4).

Expression changes of bone biomarkers

Multiple *in vivo* and *in vitro* studies have shown, that Sr doped biomaterials can stimulate osteoblast proliferation and differentiation to form a new bone (38). Changes of bone turnover is seen in expression levels of bone biomarkers. It is found, that Sr increase higher collagen synthesis and enriche precipitation of hydroxyapatite (30). It up-regulates higher expression of alkaline

phosphatase (APL), collagen type I (Col I) and OPG in animals (32). Singh et al., have found, that Sr doped biomaterials can increase expression of osteocalcin and osteopontin, both required for matrix mineralization (50). Sr is also capable of enhancing expression of BMP2 (bone morphogenic protein 2) through Wnt and MAPK signaling pathways by activating CaSRs (49). Yang et al., compared hydroxyapatite with and without Sr and found out that it induces proliferation and differentiation of osteoblasts through higher transcriptional activity of Wnt signaling and β-catenin expression (55). Strontium loaded xerogel scaffolds were used to treat critical size metaphyseal fracture defects in ovariectomized rats, where Sr group scaffolds resulted in significantly higher bone formation, higher intensity of BMP2, OPG, Col I, Runx2, osteocalcin (OC) and lower expression of RANKL (40). Similar results were published by Isaac et al., where mouse calvarial bone cell model was enriched with Sr containing bioactive glass material. They found enhanced osteoblast proliferation, greater activity of APL, higher secretion of osteocalcin, Col-I, bone sialoprotein and up-regulation of Runx2 and Osterix genes (22). Also Park et al., demonstrated that strontium modified ceramic bone graft substitute showed early osteoblast differentiation. ALP activity, OC, transcriptional factors like Runx2 and Osterix was found to be upregulated comparing with other samples without Sr (33). Moreover, presence of Sr ions can interact and down regulate release of pro-inflammatory cytokine like TNF-α (tumor necrosis factor α) and IL-1 (interleukin 1) (14). *In vitro* study of periodontal ligament cells showed that Sr is able to inhibit expression of IL-6, which plays important role in inflammation and osteoclastogenesis by up-regulating expression of RANKL and inducing bone resorption (44). Sr can also inhibit MMP2 and MMP9 (matrices metalloproteinase), which are involved in the process of tissue degradation (34). Andersen et al., found correlation between OPG and presence of CD68 on osteoclasts - when expression of OPG was increased, the expression of CD68 was absent, indicating that recruitment of osteoclast precursors are limited near the implants containing Sr (1).

Induction of angiogenesis

Strontium can stimulate neoangiogenesis, promoting proliferation and migration of endothelial cells (8). Similarly, it was found that calcium phosphate scaffolds containing Sr induced the secretion of proangiogenic factors as bFGF (basic fibroblast growth factor) and VEGF (Vascular endothelial growth factor). VEGF is an important regulator in neoangiogenesis and its expression is upregulated during the fracture repair to induce development of new blood vessels, whereas bFGF plays a pivotal role in fracture healing and bone remodeling. It may accelerate proliferation and differentiation of osteoblastic cell lineage and stimulate VEGF release from osteoblasts. This indicates that Sr promotes neovascularization and improves new bone formation (17). Chen et al., used biodegradable strontium doped calcium polyphospshate (CPP) to promote the adhesion and spread of endothelial cells. They obtained that proliferation of endothelial cells and number of migrating cells to form new blood vessels showed superior results compared to CPP group without strontium ions (9). Similar results were found using different biomaterials. Macroporus strontium substituted calcium silicate bioactive ceramic scaffold was used on osteoporotic bone regeneration for critical rat calvarial bone defect model repair. Results showed, that Sr plus group enhanced early and prolonged expression of VEGF (25).

Local effect of strontium on cells

Many cytocompatibility studies has been done to evaluate local and side effect of biomaterials containing strontium ions. Tie et al., has carried out detailed study on rabbits, where they compared pure magnesium, which was previously considered as a biocompatible and non-toxic implant material with Sr containing magnesium alloy. Hemolysis was found to be almost 3 folds higher in magnesium group for 7.13%, but Sr group showed only 2.54%. They also investigated influence of Sr on peri-implant localized toxicity and systematic toxicity of rabbits' spleen, kidney and liver. No morphological changes of nuclei of vastus lateralis muscle were found. There were no signs of necrotic tissue at all. Also no changes or inflammatory infiltrates were found in liver, spleen or kidney (52). Similar findings were stated by many other authors. Sr rich novel bioresorbable hydroxyapatite membrane biomaterial showed better bone regenerative properties and no cytotoxicity of surrounding tissue (20). Even more, Sr doped biomaterials can enhance bone cell viability in the process of healing (25) or calcium phosphate doped with strontium can increase the number of live cells in comparison to calcium phosphate alone (51). Gu et al have demonstrated, that incorporation of strontium in magnesium –zirconia implants, used for rabbit femur defects, influences osteogenesis by superior viability and proliferation of osteoblasts on implant surfaces. No adverse tissue reaction and no cytotoxic effect at various points of time using Sr was determinate (18).

Bone volume and strength changes

Querido et al., concluded that presence of Sr improves the interaction of osteoblastic cells with titanium substrates, increasing cell proliferation and differentiation into mature osteoblasts and production of bone-like mineralized matrix (39). Biocompatibility testing of Sr modified titanium implant was carried out by Liu et al., where they found, that adding Sr ions can improve spreading of osteoblasts, increase early adherent cell number and enhance osteoblasts growth through significantly enhanced expression of osteogenesis related genes and proteins on implant surface area (26). Presence of Sr also shows better bone to implant contact when compared to control groups (52) or a larger amount of new bone in the marrow space close to implant (1). Incorporation of strontium

into the hydroxyapatite gel forming system resulted in effective vertical bone expansion for rat calvarial bone augmentation compared with control group without Sr. It was demonstrated that single injection of new system may activate the progenitor cells from periosteum to increase healing time and enhance bone augmentation (20). Another study compared different bone substitutes for bone defects in trabecular region of rats' femur. Superior results of total amount of new bone formation using Sr containing hydroxyapatites (HA) was found rather than in Sr negative group. They obtained, that SrHA promotes early bone regeneration, involving reduced number of osteoclasts and downregulation of osteoclastic genes like CatK (osteoclast activity marker) and CR (osteoclasts receptor marker) and reduction of RANKL expression. Also IL-6 and TNF – α expression levels were significantly reduced in bone defects filled with SrHA (13). When added to calcium phosphate cement material, Sr showed accelerated degradation and enhanced osteoconductivity with higher rate of cell proliferation and new bone formation. Also significantly more peri-cement area of new bone and less cement residues were observed 32 weeks after the rat femur bone defect operation (23). Use of strontium modified calcium phosphate cement in critical-size metaphyseal fracture defects in ovariectomized rats showed statistically significant amount of enhanced new bone formation in the entire defect area compared to control groups. High rates of Sr were detected up to a distance of 6mm to the implant, proving that local delivery of strontium stimulates new bone formation (53). Sr enriched scaffolds improves implant bone apposition during bone formation with very little or no discontinuity between them (18). Another positive effects of Sr show that addition of strontium increases the resistance of corrosion in different scaffolds and improves mechanical properties of bone (19).

Preliminary study done by authors

Authors is conducting *in vivo* study of osteoporotic rabbit femur bone defect substitution with strontium and without strontium enriched biomaterials. Contralateral intact femur bone was set as a control. Obtained data were compared between healthy rabbits' bone and sham surgery affected bone to exclude traumatic role for bone regeneration. Results showed that number of osteoprotegerin positive cells is up-regulated when strontium within biomaterial is used, while traumatic injury and biomaterials without strontium marked notable lesser number of cells (Table 1) *(Pilmane and Zarins, unpublished data, 2016)*. The osteoporotic bone alone demonstrated just few osteoprotegerin positive cells (Figure 1-3).

CONCLUSION

Strontium enriched biomaterials shows superior results to induce osteogenesis and new bone formation up-regulating expression of biomarkers like osteoprotegerin, alkaline phosphatase, osteopontin, osteocalcin and VEGF in comparison to others without strontium. Even more, presence of strontium can decrease osteoclastogenesis and bone resorption, showing no cytotoxic effect on viable bone cells. Although use of strontium in different biomaterials have shown encouraging results, there is still not fully understood mechanisms of action. Moreover, Sr effects are dose dependent and exact dose is not established yet. There is need for further studies to provide new and precise insights into the pathophysiology of bone regeneration.

Conflict of interest: None

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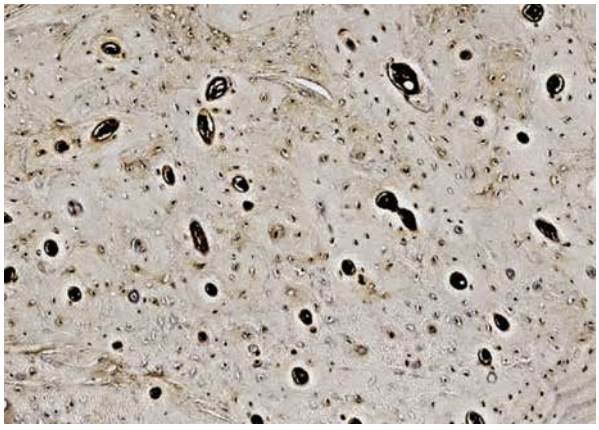

Fig. 1. Note numerous osteoprotegerin - containing osteocytes in osteoporotic rabbit bone after biomaterial and strontium implants. OPG IMH, x 150

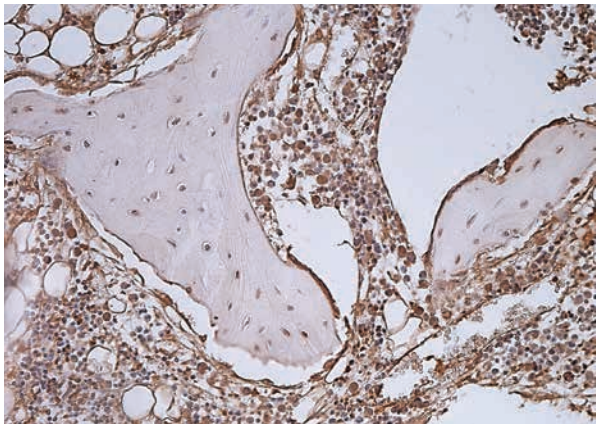

Fig. 2. Note moderate osteoprotegerin - containing positive cells in osteoporotic sham surgery bone. OPG IMH, x 200

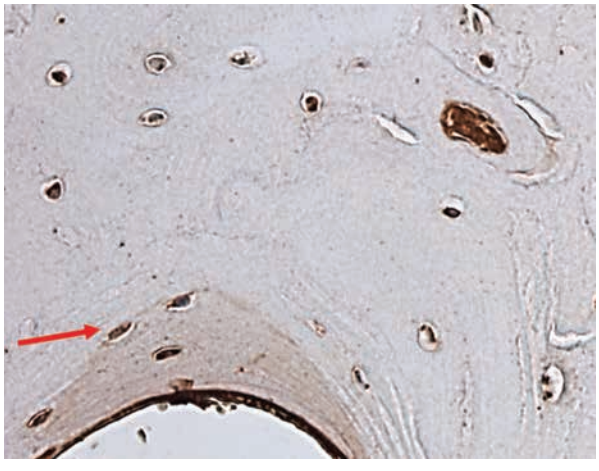

Fig. 3. Note few osteoprotegerin - containing positive osteocytes in osteoporotic rabbit bone. OPG IMH, x 200

Table 1. Comparison of osteoprotegerin containing cells between osteoporosis affected bone and such with different biomaterial implants

	Biomaterial with strontium	Biomaterial without strontium	Sham surgery	Osteoporotic bone
Number of rabbits	**7**	**7**	4	2
OPG	+ + +	+ +	+ +	+

Number of immunopositive cells were evaluated by semiquantitative method, where "+" – few positive structures in visual field; "++" – moderate positive structures in visual field; "+++" – numerous positive structures of visual field.