

# The Impact of Strontium Ranelate on Implant Osseointegration of Osteoporosis *in Vivo* Experiment

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## Abstract

**Objective:** To investigate the impact of strontium ranelate on implant osseointegration of osteoporotic rats *in vivo* experiment.

**Method:** Thirty-six female rats were randomly divided into three groups: ovariectomy group (A=12), strontium ranelate low-dose treatment group (B=12) and strontium ranelate high-dose treatment group (C=12). After the success of the osteoporosis model building, HA coated titanium implants were inserted into proximal metaphyses of tibiae, meanwhile, the rats of group B and C received oral medication of strontium ranelate (B: 450 mg/kg.d C: 900 mg/kg.d), 12 weeks after surgery, animals were killed and decalcified sections were prepared and examined histologically and histomorphometrically, as well as micro-CT examination.

**Results:** 12 weeks after implantation surgery, Bone Mineral Density (BMD), Implant Bone Contact Rate (IBCR) and New Bone Volume (NBV) in group B and C were significantly higher compared with group A ( $p < 0.01$ ).

**Conclusion:** Strontium ranelate may resist the negative influence of osteoporosis and promote osseointegration of implant.

**Keywords:** Strontium ranelate; Osteoporosis; Implant; Osseointegration; Bone mineral density; Implant bone contact rate; New bone volume

## Introduction

Dental implant restoration is one of the most important methods for tooth loss therapy. Osteoporosis (OP) has been regarded as an important risk factor for implant failure [1,2] and clinical studies have demonstrated that OP could reduce the osseointegration of implant, it is necessary to enhance the bone metabolism and inhibit excessive bone resorption on the surface of implant [3].

Strontium ranelate (SR), a new active drug shown to reduce OP, can stimulate osteoblast proliferation and inhibit osteoclast resorption, which allowing promoting bone formation while decreasing bone resorption [4-7]. SR has a good application prospect and was designed to contribute to the dental implant in postmenopausal women with OP. In recent years there was a growing number of studies investigated the effect of SR for treating OP, and the result showed that it could increase the bone weight of vertebra, humerus, and femur of animals.

However, rarely studies reported that SR was used for dental implant and increasing bone volume around the implant area in patients suffered from OP. The purpose of our study was to investigate the effect of strontium ranelate on implant osseointegration in OP rats.

## Material and Methods

### Materials

Total amount of 36 female Sprague Dawley (SD) rats (3 months old) with an average weight of 250 g were purchased from Laboratory Animal Center of Henan Province. Hydroxyapatite (HA) coated titanium implants were provided by Biomaterials Testing Center of Sichuan University. SR was purchased from Servier Company (France) and the Dual-energy X-ray absorptiometry (DEXA) was made in USA.

### OP induction in SD rats

Animals were induced through bilateral ovarian wedge resection [8] and randomly divided into three groups, the OP group (group A), the low-dose SR treatment group (group B) and the high-dose SR treatment group (Group C). Animals were given dexamethasone (0.5 mg/kg) subcutaneous injections after surgery twice a week for 12 weeks.

### Dental implantation and SR administered

12 weeks after OP induced, HA coated titanium implants were implanted into the right tibiae near metaphysical. For all the SD rats, the procedures were as follows: incised the skin and soft tissue of the right tibiae near metaphysical to expose the bone, prepared planting holes with a 2 mm-diameter dental drill, screwed the implants penetrating into the cortical bone and layered suture incisions. Conventional farming, penicillin ( $40 \times 10^4$  U/Kg) was intramuscular

administered 1 day before and everyday post-surgery for 3 days, respectively. Rats in group B (450 mg/kg a day) and C (900 mg/kg a day) were given SR orally.

### Histological observation and bone histomorphometric analysis

12 weeks after implantation, animals were sacrificed. And the tibial implants region (20 mm in length) were excised and embedded in resins. And hard tissue slices at the thickness of 4 um with undecalcification were obtained by using a slice microtome, and all the slices were stained by using methylene blue. Microstructures of the implant-bone interface (trabecular bone around implants) were observed with a micro-CT. Dual energy X-ray absorptiometry was used for measuring the bone mineral density (BMD).

The digital medical analysis system was adopted for analysis of the following parameters in the implant region:

- Implant Bone Contact Rate (IBCR %), which was the proportion of direct contact area of the implant and newly formed bone account for the total area of the implant.
- New Bone Volume (NBV %), which was the proportion of area of the new bone formed within 1 mm around the thread bottom of the implant account for the total area of this region.

### Statistical analysis

Statistical analyses were performed using the statistics package SPSS16.0. One-way ANOVA was used to compare the BMD, IBCR and NBV among the 3 groups. The level of significance was set at  $p < 0.01$ .

## Results

### The measurement of BMD, IBCR, NBV

After 12 weeks, BMD, IBCR, NBV in group B and group C were significantly higher than group A ( $p < 0.01$ ),  $*p < 0.01$  and there was a significant difference compared with the control group. But no statistically significant difference between group B and C given in the Table 1.

	BMD	IBCR (%)	NBV (%)
Group A	0.1958 ± 0.0173	43.25 ± 4.01	42.76 ± 5.66
Group B	0.2627 ± 0.0185*	67.25 ± 5.50*	73.43 ± 6.06*
Group C	0.2855 ± 0.0179*	70.05 ± 6.50*	75.78 ± 6.23*
* $p < 0.01$			

**Table 1:** comparison of each index after different dose SR was administered ( $X \pm S$ )

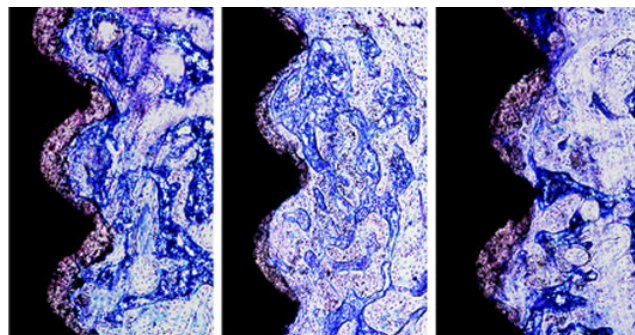
## Discussions

OP is a systemic bone disease characterized by low bone mass, damage of bone microstructure, increased bone fragility and being more vulnerable to fracture. It can be happened in different gender and age groups, especially in aged men and postmenopausal women [9]. OP which happened in postmenopausal women is a bone abnormal metabolism disease that the bone resorption outweighs bone formation accompanies estrogen deficiency. Pathological anatomy

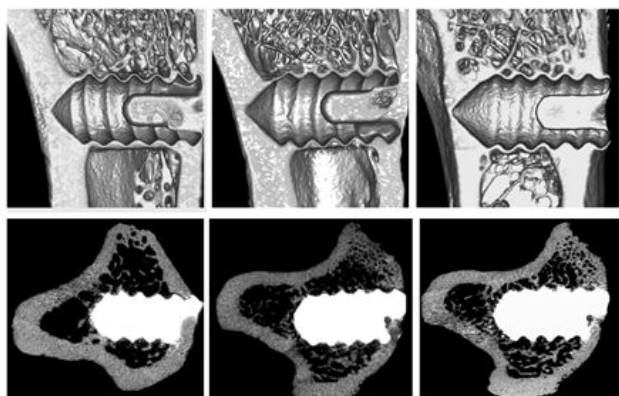
showed thinning cortical, more porous and interruptions trabecular [10]. When OP happened, the IBCR and the relative bone mass were decreased significantly in the OP area. In our study, the OP model was built in rats through bilateral ovarian wedge resection combined with dexamethasone injection.

SR, under the brand name Protelos, was developed by Servier company (France). It was a drug for OP treatment with a dual mechanism targeting decreasing bone resorption and increasing bone formation. Currently, numerous animal experiments have demonstrated that Protelos could accelerate the new bone formation and slow down the old bone resorption. Study showed that Protelos could both decrease the bone dropping in ovariectomized rats and enhance the bone density in normal animals [11]. SR has dual pharmacological effects. Regarding the proliferation of the osteoblast, the SR can increase the collagen and non-collagen protein synthesis, at the same time; it can promote the osteoblast-mediated bone formation by promoting the proliferation of the preosteoblast. Simultaneously, it can play a role in inhibiting the differentiation of the pre-osteoclast in a concentration-dependent manner, consequently inhibiting the osteoclast-mediated bone resorption. Some studies indicate that SR treatment may increase the risk of cardiac disease, but SR is not limited and it is still retained as a therapeutic option for osteoporosis. When used appropriately, it should therefore remain part of therapeutic armamentarium for osteoporosis [12].

This paper investigated the effect of different doses of SR on the Osseo integration of titanium implant in OP animals by the methods of histologic examination, micro-CT, BMD, etc. Results showed that bone trabeculae in the implant region in the low-dose group were significantly larger than group A, but less in quantity and thinner in thickness. It can be observed that the bone formation area was larger in the high-dose group. BMD, IBCR, NBV of the group B and group C significantly increased ( $P < 0.01$ ) and were higher than group A after 12 weeks ( $P < 0.01$ ). The utility of SR could minimize the negative effects of OP, promote the healing of surrounding bone implant body and increase the implant-bone contact ratio. Figure 1 (results of histologic examination) and Figure 2 (results of micro-CT) showed that with the increasing of SR dose, the bone trabecular formation and bone mass increased. Compared with the control group, the intake of SR was more, the bone formation was more. Continuous and large area of bone formation could be observed in group B and group C, and were more than group A significantly ( $P < 0.01$ ). However, there was no significant difference between group B and group C.



**Figure 1:** Implant-bone interface morphology 12 weeks after surgery (100x)



**Figure 2:** Implant bone trabecular microstructure 12 weeks after surgery

Ammann et al. [13] found that different dose Protelos (450,900 mg/kg.d) could enhance bone strength at different levels, and increase bone mass of vertebra and femur in rats. Protelos could augment the volume of the trabecular and cortical bone volume, and increase the total thickness and amount of trabecular [14]. It could also improve the basic serum Insulin-like Growth Factor (IGF) and plasma Alkaline Phosphatase (ALP) level. The SR dose adopted in our study was determined according to the previous studies and literatures review. This study has shown that the bone formation after SR intake differ significantly from the OP group. The results indicated that the different effects of different oral dose in the study were obvious. However, whether the dose is appropriate for dental implant or not need further study to explore. To obtain an ideal bone mass of the implant region, the optimum oral dose and frequency of SR should be further studied.

### Acknowledgement

This experiment on female rats was performed after taking permission from Animal Ethics Committees (AECs) and it was monitored, supervised by the head of Department of Oral Medicine, Zhengzhou University of School of Stomatology, China.

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