Micron 80 (2016) 122–134

Contents lists available at ScienceDirect

Micron

journal homepage: www.elsevier.com/locate/micron

The effects of strontium on bone mineral: A review on current knowledge and microanalytical approaches

William Querido[a], Andre L. Rossi[b], Marcos Farina[a,*]

[a] Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, 21941-902 Rio de Janeiro, RJ, Brazil
[b] Centro Brasileiro de Pesquisas Físicas, 22290-180 Rio de Janeiro, RJ, Brazil

ARTICLE INFO

Article history:
Received 11 June 2015
Received in revised form 14 October 2015
Accepted 14 October 2015
Available online 20 October 2015

Keywords:
Bone mineral
Strontium ranelate
Analytical microscopy
Nanoscale analysis
EELS
Biomineralization

ABSTRACT

The interest in effects of strontium (Sr) on bone has greatly increased in the last decade due to the development of the promising drug strontium ranelate. This drug is used for treating osteoporosis, a major bone disease affecting hundreds of millions of people worldwide, especially postmenopausal women. The novelty of strontium ranelate compared to other treatments for osteoporosis is its unique effect on bone: it simultaneously promotes bone formation by osteoblasts and inhibits bone resorption by osteoclasts. Besides affecting bone cells, treatment with strontium ranelate also has a direct effect on the mineralized bone matrix. Due to the chemical similarities between Sr and Ca, a topic that has long been of particular interest is the incorporation of Sr into bones replacing Ca from the mineral phase, which is composed by carbonated hydroxyapatite nanocrystals. Several groups have analyzed the mineral produced during treatment; however, most analysis were done with relatively large samples containing numerous nanocrystals, resulting thus on data that represents an average of many crystalline domains. The nanoscale analysis of the bone apatite crystals containing Sr has only been described in a few studies. In this study, we review the current knowledge on the effects of Sr on bone mineral and discuss the methodological approaches that have been used in the field. In particular, we focus on the great potential that advanced microscopy and microanalytical techniques may have on the detailed analysis of the nanostructure and composition of bone apatite nanocrystals produced during treatment with strontium ranelate.

1. Strontium and bones

In the last decade, we have witnessed a boom in the interest of the effects of strontium (Sr) on bone, due to the development of the promising drug strontium ranelate. This drug is used for treating osteoporosis, a major bone disease affecting hundreds of millions of elderly people worldwide, especially postmenopausal women (Reginster and Burlet, 2006; Compston, 2009; Harvey et al., 2010; Ström et al., 2011). Strontium ranelate is currently registered as a medication in over than 70 countries, having its commercial debut in Europe in 2004. The interest in the role of Sr in bone biology, however, dates from much earlier. Due to the chemical similarities between Sr and Ca, a topic that has long been of particular interest is the incorporation of Sr into bones replacing Ca from the mineral substance, which is a poorly crystalline carbonated hydroxyapatite.

In 1870, Papillon investigated changes in bone composition after feeding a pigeon with strontium phosphate and analyzing its calcined bone ash (Papillon, 1870). In this study, he described for the first time that Sr was in fact incorporated into bone. A few years later, König further showed that the incorporation of Sr into the bones of rabbits fed with strontium phosphate was coupled to a reduction of its Ca content (König, 1874). These early observations were confirmed in 1923 by the analysis of the bone ash of rats fed with strontium carbonate (Kinney and McCollum, 1923). Moreover, the authors found that the incorporation of Sr into bone occurs quite rapidly, especially in the first two weeks. They also showed that the rate of incorporation was more rapid in young than in mature rats, which was attributed to the higher metabolism of the bone tissue of the younger animals. A more focused study on how Sr could be incorporated into the bone mineral substance was described in 1951 (MacDonald et al., 1951). The authors analyzed the bone ash of rats injected with strontium chloride by using X-ray diffraction (XRD). They found that Sr caused distortions in the unit cell dimen-

* Corresponding author.
E-mail address: mfarina@icb.ufrj.br (M. Farina).

http://dx.doi.org/10.1016/j.micron.2015.10.006
0968-4328/

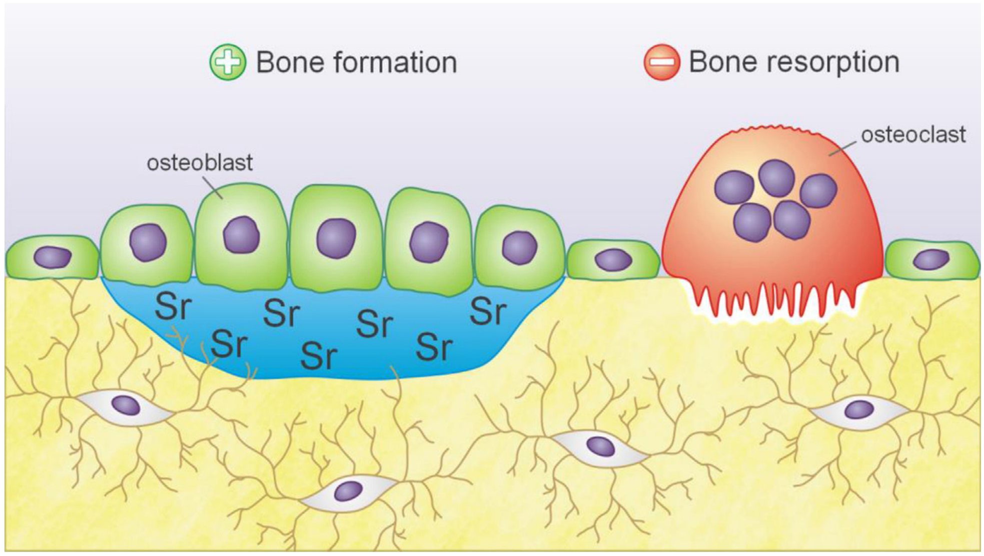

Fig. 1. Effects of strontium ranelate on bone. Strontium ranelate promotes bone formation by osteoblasts, inhibits bone resorption by osteoclasts, and leads to the incorporation of Sr into the mineralized matrix formed during treatment.

sions of the bone mineral crystals, suggesting that these ions were incorporated into the crystalline lattice structure.

The interest on all of these topics has been markedly rekindled with the development of strontium ranelate, resulting in a great number of publications on the interaction of Sr with bone mineral (Boivin et al., 1996; Dahl et al., 2001; Boivin and Meunier 2003; Farlay et al., 2005; Cazalbou et al., 2005; Li et al., 2010a; Boivin et al., 2010; Roschger et al., 2010; Doublier et al., 2011; Pemmer et al., 2011; Bazin et al., 2011; Oliveira et al., 2012; Doublier et al., 2013; Querido and Farina, 2013; Pasqualetti et al., 2013; Pemmer et al., 2013; Doublier et al., 2014; Frankær et al., 2014; Rossi et al., 2014a; Querido et al., 2014). The use of electron microscopy and microanalytical related techniques plays a key role to better understanding of the effects of Sr on bone.

2. Strontium and osteoporosis

The main characteristic of osteoporosis is the increase in bone fragility and risk of fracture caused by a reduction of bone mass and density and an impairment of bone microarchitecture (Reginster and Burlet, 2006; Compston, 2009; Harvey et al., 2010; Ström et al., 2011). The occurrence of osteoporosis is primarily associated to an imbalance in the cellular mechanisms of bone remodeling, a physiological process essential for the maintenance of bone health throughout our life (Raisz, 2005; Martin and Seeman, 2008; Marie, 2010). This process ensures that the mineralized matrix of the bone tissue is constantly renewed, being produced by osteoblast cells and resorbed by osteoclast cells. In the elderly population, especially in postmenopausal women, because of the decline in estrogen levels, this process favors bone resorption over formation, leading to an accelerated bone loss that may turn into osteoporosis.

The potential use of strontium for treating osteoporosis was first described in the 1950s. In 1952, Shorr and Carter found that treatment with strontium lactate increased bone mineralization in man, suggesting a role of strontium on improving bone formation (Shorr and Carter, 1952). A few years later, in 1959, McCaslin and Janes further showed that strontium lactate reduced bone pain and seemed to increase bone mass in patients with osteoporosis (McCaslin and Janes, 1959). Unfortunately, during that same decade, the radioactive isotope Sr-90 was released into the atmosphere after the testing of nuclear weapons, contaminating the food chain and presenting a serious health risk. As a consequence,

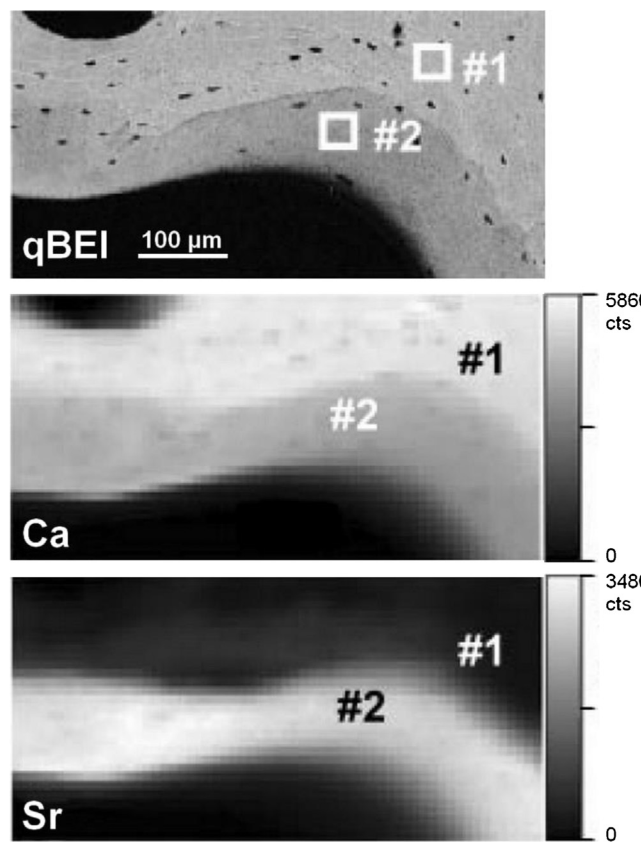

Fig. 2. Incorporation of Sr into new and old bone. Quantitative backscattered electron imaging (qBEI) allowed identifying old and new bone areas in women treated with strontium ranelate. A grey-scale contrast was obtained based on the average atomic numbers of the bone areas. The old, more mineralized bone (area #1) has brighter gray levels and the new, less mineralized bone (area #2) has darker gray levels. Synchrotron radiation induced micro X-ray fluorescence (SR-μXRF) mapping of Ca K-line shows that the new bone had less Ca, confirming its lower mineralization degree. It is clear by the mapping of Sr K-line that Sr was incorporated exclusively into the new bone formed during treatment. Images adapted from Roschger et al. (Roschger et al. 2010), with kind permission from Dr. Paul Roschger and from the publisher John Wiley and Sons.