JNT FACIT BUSINESS AND TECHNOLOGY JOURNAL
ISSN: 2526-4281 - ANO 2026 - MÊS DE AGOSTO
Ed. 76. Vol. 2 - Págs. 389-402
DOI: 10.5281/zenodo.21950405

CAPES

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

QUALIS A2

EFFECTS OF STRONTIUM ASSOCIATED WITH BIOMATERIALS ON THE MODULATION OF BONE METABOLISM: AN INTEGRATIVE REVIEW[1]

EFEITOS DO ESTRÔNCIO ASSOCIADO A BIOMATERIAIS NA MODULAÇÃO DO METABOLISMO ÓSSEO: UMA REVISÃO INTEGRATIVA

João Paulo Tavares LINHARES
Universidade Federal do Ceará (UFC)
E-mail: jptlinhares@yahoo.com.br
ORCID: http://orcid.org/0009-0003-6629-8698

Igor Iuco CASTRO-SILVA
Universidade Federal do Ceará (UFC)
E-mail: igor.iuco@sobral.ufc.br
ORCID: http://orcid.org/0000-0003-4815-6357

ABSTRACT

Bone regeneration remains a clinical challenge despite the widespread availability of implantable devices. Incorporating the strontium cation—as a substitute for calcium—into biomaterials has attracted attention due to its bioactivity and sustained release properties. This integrative review aimed to analyze the effects of incorporating strontium into biomaterials used for bone regeneration. A search of the PubMed and BVS (LILACS and SciELO) databases identified original full-text studies published between 2020 and 2025 in Portuguese, English, or Spanish, including preclinical studies on strontium-functionalized biomaterials. The primary outcomes evaluated were the intrinsic characteristics of the bioactive-biomaterial combination and the modulation of bone metabolism. Among the 15 studies utilizing in vitro and in vivo models, strontium was incorporated into biomaterials via doping, adsorption, or ionic substitution, with molar concentrations ranging from 0.26 to 50 mol%, atomic percentages from 1 to 90 at%, or weight percentages from 15 to 37 wt%. Strontium was more frequently associated with ceramics and bioglasses than with composites or polymers. Regarding biomarkers involved in cellular physiology and bone matrix formation and maturation, a dual benefit for bone gain was observed: stimulation of osteoblast-mediated anabolism and angiogenesis, alongside the reduction of osteoclast-mediated catabolism and oxidative stress. Despite promising

[1] COMO CITAR: (ABNT): LINHARES, J. P. T.; CASTRO-SILVA, I. I. Effects of Strontium Associated With Biomaterials on The Modulation of Bone Metabolism: An Integrative Review. **JNT Facit Business and Technology Journal.** Qualis A2. ISSN: 2526-4281, Mês de Agosto de 2026 - Ed. 76. VOL. 02. Págs. 389-402. Disponível: http://revistas.faculdadefacit.edu.br. Acesso em: ___/___/___.

results regarding the modulation of bone metabolism, the wide range of concentrations and applications in animal models necessitates further in-depth testing of the safety and efficacy of strontium-incorporated biomaterials in humans to standardize clinical protocols for bone regeneration.

Keywords: Strontium. Biocompatible Materials. Bone Regeneration.

RESUMO

A regeneração óssea persiste como um desafio clínico, apesar da ampla disponibilidade de dispositivos implantáveis. O cátion estrôncio em substituição ao cálcio integrado a biomateriais desperta atenção quanto à bioatividade e liberação contínua. O objetivo desta revisão integrativa foi analisar os efeitos da incorporação de estrôncio em biomateriais aplicados à regeneração óssea. Consulta às bases PubMed e BVS (LILACS e SciELO) recuperou estudos originais entre 2020 e 2025, em texto completo, em língua portuguesa, inglesa ou espanhola, incluindo estudos pré-clínicos envolvendo biomateriais funcionalizados com estrôncio. Os principais desfechos avaliados foram as características intrínsecas da associação bioativo-biomaterial e a modulação do metabolismo ósseo. Dos 15 estudos que utilizaram modelos in vitro e in vivo, houve incorporação de estrôncio nos biomateriais por dopagem, adsorção ou substituição iônica, em concentrações molares variando entre 0,26 e 50 mol%, em percentagem atômica entre 1 e 90 at% ou percentagem em peso entre 15 e 37 wt%. Houve maior associação do estrôncio a cerâmicas e biovidros do que compósitos ou polímeros. Diante dos biomarcadores envolvidos na fisiologia celular bem como na formação e maturação da matriz óssea, notou-se um beneficiamento dual para o ganho ósseo, estimulando anabolismo por osteoblastos e angiogênese e diminuindo catabolismo por osteoclastos e estresse oxidativo. Apesar dos resultados promissores na modulação do metabolismo ósseo, a multiplicidade de concentrações e aplicações voltadas a sistemas biológicos animais requerem testagem aprofundada de segurança e eficácia do estrôncio incorporado a biomateriais em seres humanos para padronização de protocolos clínicos de regeneração óssea.

Palavras-chave: Estrôncio. Materiais Biocompatíveis. Regeneração Óssea.

INTRODUCTION

Bone regeneration therapy remains a major challenge faced in Medicine and Dentistry, especially in cases of critical defects or extensive bone loss, where the

natural healing process does not occur sufficiently (Zhang *et al*, 2021; Castro-Silva *et al*, 2021). This scenario is particularly important in older populations and in patients with comorbidities such as osteoporosis, infections, or after tumor resection procedures (Castro-Silva *et al*, 2021). Traditionally, autologous bone grafting is considered the standard approach for bone reconstruction, although it has limitations such as the scarcity of available tissue and donor site morbidity (Kruppke *et al*, 2020).

Biomedical research focuses efforts on improving biomaterials as promising alternatives in tissue engineering to induce new bone formation (Castro-Silva *et al*, 2021; Naruphontjirakul; Panpisut; Patntirapong, 2023) and the association with alternative bioactives, such as the incorporation of strontium (Sr) has grown in the last decade (Costa *et al*, 2025; Luz *et al*, 2020; Luz *et al*, 2022; Luz *et al*, 2025; Soares *et al*, 2025). This divalent cation has been explored due to its ability to exert favorable in vitro and in vivo effects on bone metabolism, both in bone formation and resorption, although clinical data are a gap in literature (Costa *et al*, 2025; Luz *et al*, 2020; Luz *et al*, 2022; Luz *et al*, 2025; Soares *et al*, 2025). Due to the wide diversity of biomaterials for bone regeneration—ranging from natural or synthetic origins to ceramic, polymeric, or composite compositions—there is no consensus regarding the leading trend in Sr-containing biomaterials (Castro-Silva *et al*, 2021; Olivier *et al*, 2023; Tomasina *et al*, 2023).

Despite increasing publications reporting promising effects of Sr in different scaffolds (Olivier *et al*, 2023; Tomasina *et al*, 2023), there is great heterogeneity in the methods used, in the concentrations applied, in the experimental models employed and in the forms of ionic release which makes it difficult to standardize protocols and safe extrapolations to clinical contexts (Chan *et al*, 2025; Costa *et al*, 2025; Luz *et al*, 2020; Luz *et al*, 2022; Luz *et al*, 2025; Soares *et al*, 2025). Furthermore, many approaches still do not simultaneously consider the osteogenic and anti-resorptive effects of Sr in different bone microenvironments, as occur in conditions such as osteoporosis (Silingardi *et al*, 2024; Tang *et al*, 2024). Therefore, it is essential to integrate the most relevant findings, considering the different types of biomaterials and the functionalization strategies currently studied (Nandi *et al*, 2022). The aim of this integrative review was to analyze the effects of Sr associated with biomaterials on the modulation of bone metabolism.

METHODOLOGY

The review was structured in six stages: formulating the research question, defining inclusion and exclusion criteria, identifying relevant studies, categorizing

them, analyzing and interpreting data, and presenting a final summary of the knowledge. Based on the PICO strategy, bone regeneration was defined as the "problem," the use of Sr-containing biomaterials as the "intervention," control groups with similar biomaterials but without Sr as the "comparison," and stimulation or inhibition of bone formation as the expected "outcomes." The guiding question was: "What are the effects of incorporating Sr into biomaterials applied to bone regeneration?"

The search for articles was conducted in the electronic databases PubMed and BVS (LILACS and SciELO) on May 24, 2025. The search strategy combined the controlled MeSH/DeCS descriptors “biocompatible materials,” “strontium,” “biomaterials,” “bone regeneration” and the free terms “strontium-substituted,” “strontium-doped,” “Sr,” “osteogenesis,” “bone repair,” and “bone healing.” The Boolean operators “AND” and “OR” were used to combine the terms to maximize the sensitivity and specificity of the search.

Automatic filters were adopted from the electronic databases consulted to arrive at the following inclusion criteria: publications between 2020 and 2025 and full texts available, written in Portuguese, English or Spanish.

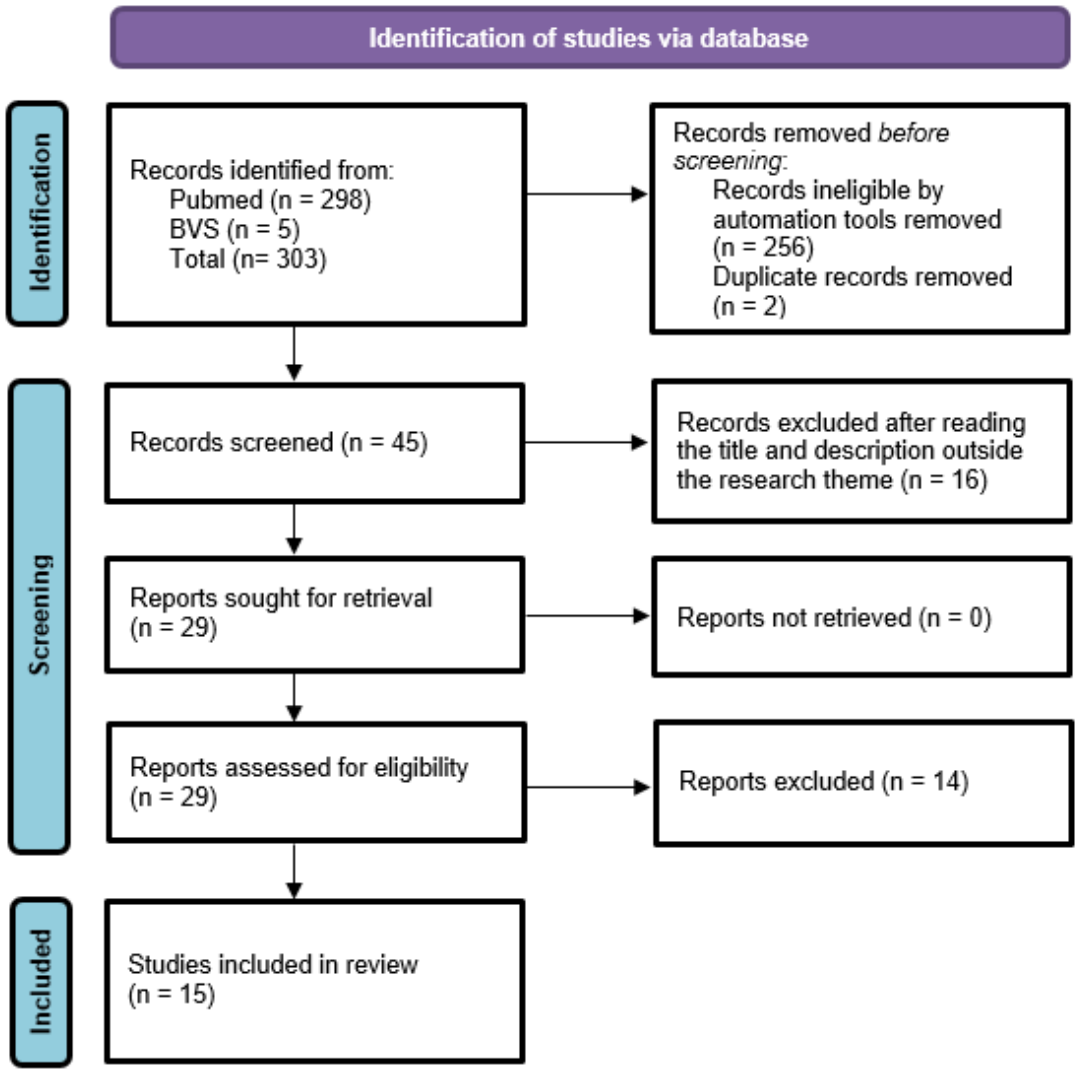
After applying the search strategy, two reviewers performed initial screening by reading the title and abstract. Subsequently, the selected articles were read in full. The content analysis revealed that original preclinical studies using Sr-incorporated biomaterials, studies evaluating osteogenic outcomes such as the expression of bone metabolism markers, bone tissue formation, or matrix mineralization, and indirect promoters such as angiogenic or antiresorptive factors were included. Studies classified as review articles, editorials, letters to the editor, or book chapters that did not have access to the full text were excluded, as were clinical studies in humans or solely laboratory studies without the use of biological systems, studies that used Sr in isolation, or focused on non-bone tissues.

Data from each article were extracted in a standardized manner, according to the following variables: author and year of publication; in vitro or in vivo experimental model; biomaterial used according to the standard classification in ceramics and bioglasses, polymers or composites; form of Sr incorporation by doping, ionic substitution, adsorption or functionalization; molar, atomic or weight concentration of Sr metal; and primary outcomes, considering increased or inhibited osteoblastogenesis, osteoclastogenesis, angiogenesis or bone matrix formation, in addition to possible secondary outcomes.

RESULTS

The selection of thematic studies followed the criteria of the PRISMA 2020 flowchart (Page *et al*, 2021), shown in Figure 1.

Figure 1: Flow diagram for integrative review.



Source: Research data.

The initial sample identified 303 articles, a number that was substantially reduced by automated filters to 256 and included the additional removal of two duplicate records. After reading the titles and abstracts, 16 articles were removed, including three exclusively metallic biomaterials, 10 off-topic articles, and three review articles. Of the 29 articles accessed in full, 14 were excluded because 11 lacked clarities regarding the method of Sr incorporation or some type of Sr concentration in the biomaterial composition, two did not evaluate bone outcomes, and one was retracted. Thus, the final sample consisted of 15 articles.

Regarding the type of study, there was a preponderance of 9 articles or 60% exclusively in vitro (Chen; Zhao; Jiang, 2021; Cirillo *et al*, 2021; Galván-Chacón *et al*,

2021; Lin; Huang, 2022; Matic *et al*, 2024; Naruphontjirakul; Panpisut; Patntirapong, 2023; Silingardi *et al*, 2024; Teterina *et al*, 2021; Tomasina *et al*, 2023) in comparison to 4 articles or 27% in vitro/in vivo studies (Jiang *et al*, 2022; Kruppke *et al*, 2020; Tang *et al*, 2024; Zhang *et al*, 2021) and 2 articles or 13% only in vivo (Nandi *et al*, 2022; Tang *et al*, 2024).

In studies involving some in vitro stage, techniques were used to analyze the most evident biological behavior in mesenchymal stem cells (MSCs) of human or murine origin (Cirillo *et al*, 2021; Galván-Chacón *et al*, 2021; Jiang *et al*, 2022; Kruppke *et al*, 2020; Matic *et al*, 2024; Silingardi *et al*, 2024; Teterina *et al*, 2021; Tomasina *et al*, 2023) and more discreetly, in differentiated adult cells of murine pre-osteoblastic lineage (MC3T3-E1) (Lin; Huang, 2022; Naruphontjirakul; Panpisut; Patntirapong, 2023; Tang *et al*, 2024; Zhang *et al*, 2021) with some isolated cases of human osteosarcoma lineages (MG-63) (Chen; Zhao; Jiang, 2021), human umbilical vein endothelial cells (EA.hy926) (Matic *et al*, 2024), human primary osteoclasts (hOC) (Cirillo *et al*, 2021), human monocytes (hMc) (Kruppke *et al*, 2020) and mouse monocytes (RAW) (Lin; Huang, 2022).

As in vivo models for implantation of Sr-containing biomaterials, orthotopic tests were basically used at the site of induced bone injury, including critical defects in rat calvaria (Jiang *et al*, 2022), metaphyseal defects in femurs of healthy rats (Olivier *et al*, 2023) or ovariectomized rats with osteoporosis (Kruppke *et al*, 2020), defects in the tibia of healthy rats (Tang *et al*, 2024), bone defects in the femoral condyle (Zhang *et al*, 2021) or tibia of healthy rabbits (Nandi *et al*, 2022). There has been only one report of ectopic implantation testing in subcutaneous tissue of athymic nude mice (Zhang *et al*, 2021).

Regarding the biomaterials used, there was an evident predominance of the ceramic (Cirillo *et al*, 2021; Galván-Chacón *et al*, 2021; Jiang *et al*, 2022; Silingardi *et al*, 2024; Teterina *et al*, 2021; Zhang *et al*, 2021) and bioglasses (Chen; Zhao; Jiang, 2021; Matic *et al*, 2024; Naruphontjirakul; Panpisut; Patntirapong, 2023; Tang *et al*, 2024; Tomasina *et al*, 2023) compared to ceramic-polymer composites (Kruppke *et al*, 2020; Naruphontjirakul; Panpisut; Patntirapong, 2023; Olivier *et al*, 2023; Tomasina *et al*, 2023) or polymers alone (Lin; Huang, 2022). Hydroxyapatite (Cirillo *et al*, 2021; Jiang *et al*, 2022; Silingardi *et al*, 2024) was the single most widely used ceramic as a matrix for the sustained release of Sr, compared to bioactive glasses (Naruphontjirakul; Panpisut; Patntirapong, 2023; Tang *et al*, 2024)—also available in mesoporous (Matic *et al*, 2024; Tomasina *et al*, 2023) or silicate (Chen; Zhao; Jiang, 2021) forms—and calcium phosphates at various stages of precipitation (Galván-

Chacón *et al*, 2021; Teterina *et al*, 2021), such as brushite (Nandi *et al*, 2022) or mineralized bovine bone (Zhang *et al*, 2021).

Composites were the most versatile biomaterials in the associations, including the polymeric components alginate and phosphates (Naruphontjirakul; Panpisut; Patntirapong, 2023), gelatin (Kruppke *et al*, 2020), carbon (Olivier *et al*, 2023) or poly(ethylene oxide terephthalate)/poly(butylene terephthalate) (PEOT/PBT) (Tomasina *et al*, 2023). The only case of polymeric biomaterial was made up of a blend of gelatin and poly-lactic-co-glycolic acid (PLGA), seeking structural synergy with Sr (Lin; Huang, 2022).

When analyzing the synthesis characteristics, the main forms of strontium incorporation were ionic doping, when Ca^{2+} cations are partially replaced by Sr^{2+} in the samples (Cirillo *et al*, 2021; Galván-Chacón *et al*, 2021; Jiang *et al*, 2022; Matic *et al*, 2024; Tang *et al*, 2024; Teterina *et al*, 2021), direct chemical substitution using strontium as the main constituent (Chen; Zhao; Jiang, 2021; Kruppke *et al*, 2020; Lin; Huang, 2022), immersion where the ready biomaterial is immersed in Sr solution (Chen; Zhao; Jiang, 2021; Kruppke *et al*, 2020; Lin; Huang, 2022) and surface functionalization in which the sample is coated with Sr particles (Olivier *et al*, 2023; Tomasina *et al*, 2023).

There was variation in the ways in which Sr concentrations were expressed in the samples. A very heterogeneous variation was observed for molar concentration between 0.26 mol% (Matic *et al*, 2024) and 50 mol% (Galván-Chacón *et al*, 2021). In atomic percentages, a variation was observed between 1 at.% (Teterina *et al*, 2021) and 90 at.% (Kruppke *et al*, 2020). In relation to the percentage by weight (%), the variation was between 15 wt% (Tomasina *et al*, 2023) and 37 wt% (Naruphontjirakul; Panpisut; Patntirapong, 2023).

The most important and recurrent outcome among studies reflecting the positive biological impact of Sr was the increase in osteoblastic activity (Cirillo *et al*, 2021; Galván-Chacón *et al*, 2021; Kruppke *et al*, 2020; Lin; Huang, 2022; Matic *et al*, 2024; Nandi *et al*, 2022; Naruphontjirakul; Panpisut; Patntirapong, 2023; Silingardi *et al*, 2024; Tang *et al*, 2024; Tomasina *et al*, 2023; Zhang *et al*, 2021), evidenced by increased cell proliferation or viability (Chen; Zhao; Jiang, 2021; Cirillo *et al*, 2021; Galván-Chacón *et al*, 2021; Kruppke *et al*, 2020; Lin; Huang, 2022; Matic *et al*, 2024; Naruphontjirakul; Panpisut; Patntirapong, 2023; Silingardi *et al*, 2024; Tang *et al*, 2024; Zhang *et al*, 2021) or metabolic increase in the expression of biomarkers.

It is possible to notice by the modulation of Sr an increase in osteoblast differentiation transcription factors RUNX2 (Cirillo *et al*, 2021; Silingardi *et al*, 2024)

and Osterix (Silingardi *et al*, 2024), bone morphogenetic protein (BMP-2) with osteoinductive capacity (Jiang *et al*, 2022; Kruppke *et al*, 2020), enzyme alkaline phosphatase related to biomineralization (Cirillo *et al*, 2021; Galván-Chacón *et al*, 2021; Matic *et al*, 2024; Silingardi *et al*, 2024; Zhang *et al*, 2021), collagen I protein as the main organic component of osteoid and early phases of osteogenesis (Cirillo *et al*, 2021; Jiang *et al*, 2022; Silingardi *et al*, 2024), osteopontin protein and bone sialoprotein present throughout the formation of bone matrix (Jiang *et al*, 2022) and osteocalcin protein encoded by the BGLAP gene indicative of bone tissue maturation (Cirillo *et al*, 2021; Jiang *et al*, 2022; Matic *et al*, 2024; Tomasina *et al*, 2023).

As a contributory phenomenon to osteogenesis, angiogenesis was also evidenced by the increased expression of vascular endothelial growth factor (VEGF) and angiopoietin-1 (ANG-1), responsible for regulating the development and maintenance of blood vessels (Jiang *et al*, 2022), by stimulating endothelial proliferation (Matic *et al*, 2024) or by the microvasculature present in the Haversian systems (Nandi *et al*, 2022).

Qualitative or quantitative histological analysis demonstrated a general trend towards increased mineralization of the extracellular matrix (Galván-Chacón *et al*, 2021; Jiang *et al*, 2022; Kruppke *et al*, 2020; Lin; Huang, 2022; Olivier *et al*, 2023; Tomasina *et al*, 2023) and the total amount of new bone formed in situ (Jiang *et al*, 2022; Kruppke *et al*, 2020; Nandi *et al*, 2022; Olivier *et al*, 2023; Tang *et al*, 2024; Zhang *et al*, 2021), with osteogenesis directly related to the anabolic processes of osteoblastogenesis, angiogenesis and bone matrix formation. There are reports on the ability of Sr to act on TGF-β signaling pathways and integrin activation, which favors greater cell adhesion and subsequent matrix deposition (Cirillo *et al*, 2021).

On the other hand, Sr inhibited osteoclastogenesis, verified through metabolic decrease of the receptor activator of nuclear factor kappa-B ligand (RANKL) pathway which is decisive in the differentiation of pre-osteoclasts into functional osteoblasts responsible for bone resorption when in greater proportion than its competitive antagonist osteoprotegerin, a natural inhibitor of osteoclastic action (Kruppke *et al*, 2020; Silingardi *et al*, 2024). This behavior could be associated as an indirect factor of overstimulation of osteoblastic action in bone tissue (Cirillo *et al*, 2021; Kruppke *et al*, 2020; Lin; Huang, 2022; Silingardi *et al*, 2024).

The inhibition of osteoclastogenesis by Sr was also evidenced by the underexpression of the enzyme cathepsin K—explaining the reduced proteolytic activity against bone collagen—and the ACP5 gene, which physiologically encodes the enzyme tartrate-resistant acid phosphatase (TRAP), responsible for matrix

demineralization; this corroborates the low staining of differentiated osteoclasts as purple, TRAP-positive, multinucleated cells (Cirillo *et al*, 2021).

Outside of the primary outcomes, a noteworthy secondary outcome related to the modulation of catabolic metabolism is the dose-dependent antioxidant effect performed by Sr, which drastically reduced free radical formation by more than half compared to the control and could explain the increased viability in murine embryonic mesenchymal cells C3H/10T1/2 (Teterina *et al*, 2021).

Table 1 summarizes the main findings of the studies with Sr selected for this review.

Table 1: Studies on effects of strontium associated with biomaterials on the modulation of bone metabolism.

Source	Experimental model	Carrier biomaterial	Effects of Sr^{2+} release
Kruppke et al. (2020)	In vitro (MSC/hMc) and in vivo (osteoporotic rat femur)	Gelatin and Ca/Sr phosphate	Increased osteoblastogenesis, decreased osteoclastogenesis and bone matrix formation
Chen; Zhao; Jiang, (2021)	In vitro (MG-63)	Sr silicate phosphate	Increased osteoblastogenesis
Cirillo et al. (2021)	In vitro (co-culture MSC/hOC)	Hydroxyapatite	Increased osteoblastogenesis and decreased osteoclastogenesis
Galván-Chacón et al. (2021)	In vitro (MSC)	Calcium phosphate microparticles	Increased osteoblastogenesis
Teterina et al. (2021)	In vitro (MSC)	Octacalcium phosphate	Proliferation and antioxidant action in undifferentiated cells
Zhang et al. (2021)	In vitro (MC3T3-E1) and in vivo (mice subcutaneous tissue and rabbit femur)	Bovine bone ceramics	Increased osteoblastogenesis and increased bone matrix formation
Jiang et al. (2022)	In vitro (MSC) and in vivo (rat calvaria)	Hydroxyapatite	Increased osteoblastogenesis, angiogenesis and bone matrix formation
Lin; Huang (2022)	In vitro (MC3T3-E1, RAW 264.7)	Gelatin and PLGA	Increased osteoblastogenesis, decreased osteoclastogenesis
Matic et al. (2024)	In vitro (MSC, EA.hy926)	Mesoporous bioactive glass nanoparticles	Increased osteoblastogenesis and angiogenesis
Nandi et al. (2022)	In vivo (rabbit tibia)	Brushite	Increased osteoblastogenesis, angiogenesis and bone matrix formation
Naruphontjirakul; Panpisut; Patntirapong (2023)	In vitro (MC3T3-E1)	Alginate and bioactive glass nanoparticles	Increased osteoblastogenesis and bone matrix formation
Olivier et al. (2023)	In vivo (rat femur)	Carbon with Sr-Apatite	Increased bone matrix formation
Tomasina et al. (2023)	In vitro (MSC)	PEOT/PBT with nanohydroxyapatite or mesoporous bioactive glass	Increased osteoblastogenesis and bone matrix formation
Tang et al. (2024)	In vitro (MC3T3-E1) and in vivo (rat tibia)	Phosphate glass	Increased bone matrix formation

Silingardi et al. (2024)	In vitro (MSC)	Hydroxyapatite	Decreased osteoclastogenesis and increased angiogenesis

Source: Research data.

DISCUSSION

The biocompatibility of Sr is commonly verified in literature (Costa *et al*, 2025; Luz *et al*, 2020; Luz *et al*, 2022; Luz *et al*, 2025; Soares *et al*, 2025) and confirms the findings of this review. In vitro studies did not indicate representative cell death, despite short-term inhibition of proliferation or metabolism for osteoclasts, which suggests its biological safety and reversibility of the condition, not permanently interfering with bone remodeling (Cirillo *et al*, 2021; Kruppke *et al*, 2020; Lin; Huang, 2022; Silingardi *et al*, 2024). In addition to pharmacodynamic studies in bone tissue, literature lacks more in-depth pharmacokinetic studies in biotransformation organs such as kidneys and liver to rule out any risk of toxicity (Costa *et al*, 2025).

Strontium bioactivity was also evident by pleiotropic effects in different tissues when Sr was incorporated into scaffolds (Cirillo *et al*, 2021; Tomasina *et al*, 2023). The effects of Sr on the stimulation of osteoblast anabolism (Chen; Zhao; Jiang, 2021; Cirillo *et al*, 2021; Galván-Chacón *et al*, 2021; Jiang *et al*, 2022; Kruppke *et al*, 2020; Lin; Huang, 2022; Nandi *et al*, 2022; Naruphontjirakul; Panpisut; Patntirapong, 2023; Tomasina *et al*, 2023; Zhang *et al*, 2021) and new blood vessels (Jiang *et al*, 2022; Matic *et al*, 2024; Nandi *et al*, 2022; Silingardi *et al*, 2024) and inhibition of osteoclastic catabolism (Cirillo *et al*, 2021; Kruppke *et al*, 2020; Lin; Huang, 2022; Silingardi *et al*, 2024) corroborate the greater formation of extracellular matrix (Jiang *et al*, 2022; Kruppke *et al*, 2020; Nandi *et al*, 2022; Naruphontjirakul; Panpisut; Patntirapong, 2023; Olivier *et al*, 2023; Tang *et al*, 2024; Tomasina *et al*, 2023; Zhang *et al*, 2021), confirming its participation at different levels in the bone regenerative process. The antagonistic effect of Sr on free radicals deserves further study (Teterina *et al*, 2021), to mitigate oxidative stress resulting from the inflammatory process and promote bone repair (Costa *et al*, 2025).

Among the techniques analyzed, doping during material synthesis was the one that presented the most uniform responses. In studies with ceramics, direct Sr doping showed more consistent effects than simple immersion or surface coating methods (Cirillo *et al*, 2021; Jiang *et al*, 2022). PEOT/PBT scaffolds containing Sr-doped bioactive particles showed quite satisfactory mechanical and ionic release stability (Tomasina *et al*, 2023). Incorporation via microfluidics, a technique that allows controlling very small droplets or flows, mixing precursors with enormous precision, also stood out for ensuring homogeneous distribution and particles with surface areas suitable for cellular interaction, although it requires more advanced

technologies (Galván-Chacón *et al*, 2021). Homogeneously doped biomaterials showed better long-term results, with controlled release of Sr and maintenance of bioactivity over time (Jiang *et al*, 2022; Matic *et al*, 2024). In samples that received surface adsorption, as observed with bovine bone ceramic, the initial desorption was very fast, which can lead to concentration peaks and subsequent drop in effect, an undesirable behavior for stable bone regeneration (Zhang *et al*, 2021).

The ideal dose of Sr remains a matter of debate. Studies indicate that very low concentrations, such as 0.26 mol%, already promote biological gains, but the most striking responses occurred between 5 and 10 mol% in hydroxyapatites and between 6 and 7.5 mol% in functionalized matrices (Cirillo *et al*, 2021; Jiang *et al*, 2022; Olivier *et al*, 2023). Above 20 mol% there have been reports of less predictable effects, suggesting that there is a therapeutic range to be respected to avoid toxicity or loss of integration (Cirillo *et al*, 2021; Jiang *et al*, 2022; Teterina *et al*, 2021). Desorption rates varied widely, ranging from 10% to 70% Sr release in periods between 7 and 28 days (Matic *et al*, 2024; Zhang *et al*, 2021). Biomaterials that maintained gradual release, without large peaks, such as mesoporous bioactive glass particles, favored a more stable osteogenic environment (Matic *et al*, 2024). On the other hand, in porous ceramics obtained via immersion, there was a very intense initial release, which may have contributed to less consistent cellular responses (Zhang *et al*, 2021).

Another factor that could explain the variability in the results found in the literature is the composition of the matrix used. Bioceramics, in general, allowed higher Sr concentrations without loss of structural integrity (Teterina *et al*, 2021). Biopolymers such as alginate and gelatin could have a structural advantage in adapting to complex defects, but greater caution was taken in stabilizing Sr to avoid rapid desorption, which would compromise their efficiency (Lin; Huang, 2022; Naruphontjirakul; Panpisut; Patntirapong, 2023).

In vivo experiments confirmed greater bone deposition and better integration rates in materials with controlled release and intermediate concentrations of Sr, as in femoral defect models in osteoporotic rats (Kruppke *et al*, 2020) and in studies with hybrid scaffolds (Nandi *et al*, 2022). These results clearly indicate that efficacy does not depend solely on the presence of Sr, but on the balance between its dose and the release kinetics over time (Cirillo *et al*, 2021; Jiang *et al*, 2022; Matic *et al*, 2024; Olivier *et al*, 2023; Teterina *et al*, 2021; Zhang *et al*, 2021). Such preclinical findings strengthen the clinical applicability of Sr-conjugated biomaterials, although extrapolation of results is still premature before randomized studies as predicted by the pyramid of scientific evidence levels (Zhang *et al*, 2022).

Overall, the data suggest that the appropriate choice of biomaterial and Sr incorporation technique is as relevant as the presence of the element itself (Cirillo *et al*, 2021; Galván-Chacón *et al*, 2021; Jiang *et al*, 2022; Matic *et al*, 2024; Tomasina *et al*, 2023; Zhang *et al*, 2021). The literature converges on the importance of homogeneous doping, concentrations between 5 and 10 mol% and gradual release strategies as key elements for the success of future clinical applications in bone regeneration (Cirillo *et al*, 2021; Jiang *et al*, 2022; Matic *et al*, 2024; Olivier *et al*, 2023; Tomasina *et al*, 2023). The set of findings strengthens the idea that Sr is more than a simple additive, but an active modulator of the bone microenvironment (Costa *et al*, 2025; Luz *et al*, 2020; Luz *et al*, 2022; Luz *et al*, 2025; Soares *et al*, 2025).

CONCLUSION

This integrative review consistently demonstrates that biomaterials associated with strontium have potential for applications in bone regeneration, combining anabolic and antiresorptive effects. The evidence shows that success is directly linked to the incorporation method and the definition of safe concentrations, highlighting the importance of homogeneous doping strategies and intermediate Sr ranges to ensure stable biological performance. These findings clearly point to strontium as a relevant modulator in bone engineering and indicate the need for clinical studies to consolidate its use.

REFERENCES

CASTRO-SILVA, I. I. *et al*. Pesquisa odontológica brasileira em regeneração óssea guiada: um estudo bibliométrico de quatro décadas. **Research, Society and Development**, v. 10, n. 2, p. e25510212504, 2021. http://dx.doi.org/10.33448/rsd-v10i2.12504.

CHAN, R. S. M. *et al*. Engineered 3D-printable nanohydroxyapatite biocomposites with cold plasma-tailored surface features to boost osseointegration. **ACS Applied Materials & Interfaces**, v. 17, n. 16, p. 23522-23535, 2025. https://doi.org/10.1021/acsami.4c22032.

CHEN, D.; ZHAO, J.; JIANG, X. Synthesis and characterization of silver substituted strontium phosphate silicate apatite using solid-state reaction for osteoregenerative applications. **Bioengineered**, v. 12, n. 1, p. 1111-1125, 2021. https://doi.org/10.1080/21655979.2021.1899670.

CIRILLO, M. *et al*. Strontium substituted hydroxyapatite with β-lactam integrin agonists to enhance mesenchymal cells adhesion and to promote bone regeneration. **Colloids and Surfaces B Biointerfaces**, v. 200, p. 111580, 2021. https://doi.org/10.1016/j.colsurfb.2021.111580.

COSTA, J. D. *et al*. Evaluation of toxicity, local biocompatibility, biodegradation, and systemic metabolism of cellulose/alginate/strontium apatite membranes implanted subcutaneously in mice. **Acta Cirúrgica Brasileira**, v. 40, p. e401925, 2025. https://doi.org/10.1590/acb401925.

GALVÁN-CHACÓN, V. P. *et al*. Droplet microfluidics as a tool for production of bioactive calcium phosphate microparticles with controllable physicochemical properties. **Acta Biomaterialia**, v. 128, p. 486-501, 2021. https://doi.org/10.1016/j.actbio.2021.04.029.

JIANG, S. *et al*. Synergistic effect of micro-nano-hybrid surfaces and Sr doping on the osteogenic and angiogenic capacity of hydroxyapatite bioceramics scaffolds. **International Journal of Nanomedicine**, v. 17, p. 783-797, 2022. https://doi.org/10.2147/IJN.S345357.

KRUPPKE, B. *et al*. Gelatin-modified calcium/strontium hydrogen phosphates stimulate bone regeneration in osteoblast/osteoclast co-culture and in osteoporotic rat femur defects – in vitro to in vivo translation. **Molecules**, v. 25, n. 21, p. 5103, 2020. https://doi.org/10.3390/molecules25215103.

LIN, S.-J.; HUANG, C.-C. Strontium peroxide-loaded composite scaffolds capable of generating oxygen and modulating behaviors of osteoblasts and osteoclasts. **International Journal of Molecular Sciences**, v. 23, n. 11, p. 6322, 2022. https://doi.org/10.3390/ijms23116322.

LUZ, E. P. C. G. *et al*. Resorbable bacterial cellulose membranes with strontium release for guided bone regeneration. **Materials Science and Engineering C-Materials for Biological Applications**, v. 116, p. 111175, 2020. https://doi.org/10.1016/j.msec.2020.111175.

LUZ, E. P. C. G. *et al*. Implantable matrixes of bacterial cellulose and strontium apatite: Preclinical analysis of cytotoxicity and osteoconductivity. **Materials Today Communications**, v. 33, p. 104871, 2022. https://doi.org/10.1016/j.mtcomm.2022.104871.

LUZ, E. P. C. G. *et al*. Development and evaluation of 3D printing inks based on bacterial cellulose/alginate functionalized with sodium alendronate or strontium apatite. **Materials Today Communications**, v. 44, p. 111965, 2025. https://doi.org/10.1016/j.mtcomm.2025.111965.

MATIC, T. *et al*. Multifunctional Sr, Mg-doped mesoporous bioactive glass nanoparticles for simultaneous bone regeneration and drug delivery. **International Journal of Molecular Sciences**, v. 25, n. 15, p. 8066, 2024. https://doi.org/10.3390/ijms25158066.

NANDI, S. K. *et al*. In vivo biocompatibility of SrO and MgO doped brushite cements. **Journal of Biomedical Materials Research Part B Applied Biomaterials**, v. 111, n. 3, p. 599-609, 2022. https://doi.org/10.1002/jbm.b.35177.

NARUPHONTJIRAKUL, P.; PANPISUT, P.; PATNTIRAPONG, S. Zinc and strontium-substituted bioactive glass nanoparticle/alginate composites scaffold for bone regeneration. **International Journal of Molecular Science**, v. 24, n. 7, p. 6150, 2023. https://doi.org/10.3390/ijms24076150.

OLIVIER, F. *et al*. Long-term fate and efficacy of a biomimetic (Sr)-apatite-coated carbon patch used for bone reconstruction. **Journal of Functional Biomaterials**, v. 14, n. 5, p. 246, 2023. https://doi.org/10.3390/jfb14050246.

PAGE, M. J. *et al*. The Prisma 2020 statement: an updated guideline for reporting systematic reviews. **BMJ**, v. 372, n. 71, p. 1-9, 2021. https://doi.org/10.1136/bmj.n71.

SILINGARDI, F. *et al*. Regulation of osteogenesis and angiogenesis by cobalt, manganese and strontium doped apatitic materials for functional bone tissue regeneration. **Biomaterials Advances**, v. 163, p. 213968, 2024. https://doi.org/10.1016/j.bioadv.2024.213968.

SOARES, A. L. B. *et al*. Composite Based on Biomineralized Oxidized Bacterial Cellulose with Strontium Apatite for Bone Regeneration. **Polysaccharides**, v. 6, n. 1, p. 23, 2025. https://doi.org/10.3390/polysaccharides6010023.

TANG, T. *et al*. Titanium-doped phosphate glasses containing zinc and strontium applied in bone regeneration. **Journal of Materials Science: Materials in Medicine**, v. 35, n. 1, p. 33, 2024. https://doi.org/10.1007/s10856-024-06804-z.

TETERINA, A. Y. *et al*. Octacalcium phosphate for bone tissue engineering: synthesis, modification, and in vitro biocompatibility assessment. **International Journal of Molecular Sciences**, v. 22, n. 23, p. 12747, 2021. https://doi.org/10.3390/ijms222312747.

TOMASINA, C. *et al*. Incorporation of strontium-containing bioactive particles into PEOT/PBT electrospun scaffolds for bone tissue regeneration. **Biomaterials Advances**, v. 149, p. 213406, 2023. https://doi.org/10.1016/j.bioadv.2023.213406.

ZHANG, C. *et al*. Bone induction and defect repair by true bone ceramics incorporated with rhBMP-2 and Sr. **Journal of Materials Science: Materials in Medicine**; v. 32, n. 9, p. 107, 2021. https://doi.org/10.1007/s10856-021-06587-7.

ZHANG, K. *et al*. Evidence-based biomaterials research. **Bioactive Materials**, v. 15, p. 495-503, 2022. https://doi.org/10.1016/j.bioactmat.2022.04.014.