Effect of Strontium-Coated Titanium Implants on Osseointegration in Animal Models: A Literature Systematic Review

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Purpose: This study represents a systematic review of the literature to assess the effectiveness of strontium-coated titanium surfaces on osseointegration in experimental assays with healthy, nonosteoporotic and/or nonosteopenic animals. Materials and Methods: An electronic search was conducted of the databases MEDLINE/PubMed, Wiley Library, and Web of Science through 2018, with the aim of identifying studies on the osseointegration of titanium implants modified with strontium. Results: A total of 255 papers were found, of which 11 were included in this systematic review. The primary result was the percentage of bone-to-implant contact (BIC) around the titanium implants with or without a strontium-coated surface. The different techniques used to coat titanium surfaces with strontium recorded significant results in terms of the improvement in the implant’s quality, as they increased its contact with the bone, bone area, and bone formation, as well as enhanced its biomechanical properties. Conclusion: Nine of 11 studies reported that titanium implants coated with strontium showed significantly higher BIC (P < .001 to P < .05). This coating also improved the implants’ biomechanical properties. Int J Oral Maxillofac Implants 2019;34:1389–1396.

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Keywords: animal model, osseointegration, strontium, surface modification, titanium implant

Since Brånemark et al published the first research into osseointegration, dental implants have become the most predictive method for replacing lost teeth.1 Albrektsson et al established six conditions that may have an impact on the success of osseointegration: the implant’s material, design, and surface, together with the state of the bone, the surgical technique, and the prosthetic load.2

Titanium is the material of choice for dental implants and orthopedic prostheses. The surface is passive, forming an oxide layer that improves osseointegration. Although many implants today have a sandblasted, large-grit, acid-etched (SLA) surface, a number of different physical, chemical, and biologic modifications are being studied,3 such as the implementation of bioactive ions and standardized protocols for insertion and loading in specific clinical applications, recording highly predictable results.4 Research into different experimental models has prompted the use of sundry metals for modifying implant surfaces, such as calcium, magnesium, and strontium, and thereby optimizing osseointegration.5–7 Anti-osteoporotic drugs have even been proposed as a coating for titanium implants for facilitating better integration.8 The effect of strontium on bone growth at the bone-implant interface has been reported in a number of studies in the literature,7,9 along with functionalized titanium surfaces involving the continual release of strontium.10 Stable strontium is a nonradioactive and nontoxic oligo-element that is essential in the human skeleton,

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and is considered a promising material for improving osseointegration, with effects on osteogenic gene expression, cellular differentiation, and increased bone apposition when included in, for example, bioreabsorbable alloys, cements, bioglass, composites, and surface coatings.\(^\text{11}\)

The mechanisms through which strontium affects bone remodeling, with a double impact on osteoblasts and osteoclasts, remain a mystery. In vitro results have shown that in clinical use, strontium ranelate acts upon the osteogenic differentiation of mesenchymal stem cells.\(^\text{12}\) In addition, it reduces the adherence of osteoclasts to the bone, impacting upon bone-forming cells through the differentiation of osteoblasts, by increasing alkaline phosphatase activity and collagen synthesis.\(^\text{13}\)

Nevertheless, Europe’s Pharmacovigilance Risk Assessment Committee (PRAC) issued a statement on April 16, 2013 recommending a restriction on the use of strontium ranelate in patients with a history of ischemic cardiomyopathy or chronic high blood pressure.\(^\text{14}\)

A series of techniques have been described for the chemical and topographic modification of titanium surfaces. According to some scholars, the plasma electrolytic oxidation system, with layers of oxide and a high strontium content, would improve osseointegration capacity thanks to the presence of strontium ions on the implant surface.\(^\text{15}\) Hydrothermal treatment is a simple and effective way of adding strontium to the titanium surface in the form of an oxide layer.\(^\text{15,16}\) The co-sputtering process produces coatings that include strontium and oxygen, leading to good mechanical stability and predictable strontium release values.\(^\text{7}\)

The aim of the present study was to conduct a literature systematic review and compare the efficacy of strontium-coated titanium surfaces more conducive to osseointegration? To answer this question, a population of animals receiving endosseous implants where the intervention consisted of strontium-coated titanium implants was chosen. The controls were titanium implants without a strontium coating, and the outcomes revised in the literature were bone-to-implant contact (BIC), percentage of bone formation (BF%), bone area (BA), and biomechanical test (BT).

### Search Method for Identifying Studies

An electronic search for scientific articles was conducted using the databases MEDLINE/PubMed, Wiley Library, and Web of Science through 2018. The following keywords were used in the search: “titanium implant,” “strontium surfaces,” and “osseointegration.”

### Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) in vivo assays involving healthy, nonosteoporotic, and/or non-osteopenic animals; (2) testing of BIC, BA, and BF%; and (3) BT.

The exclusion criteria were as follows: (1) assays that assess the modified effect of the titanium surface, combining strontium and other elements (hydroxyapatite, calcium, magnesium, phosphate, zinc, silver, etc); (2) in vitro assays; (3) assays involving osteoporotic or osteopenic animals; and (4) systematic reviews and irrelevant, repeated studies, and those that did not meet the specified inclusion criteria.

### Data Extraction and Analysis

The articles that did not refer to the research question were discarded, and the titles and abstracts of the selected articles were obtained and included in a Microsoft Excel spreadsheet. Two reviewers (N.L.-V. and J.M.-F.) separately selected the titles and abstracts. Any disagreement over the choice of articles was resolved through a discussion between these two reviewers. Complete versions of the selected articles were then obtained for their review and inclusion.

### Risk of Bias of the Selected Articles

The risk of bias (RoB) tool provided by SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) was used accordingly.\(^\text{17}\)

### MATERIALS AND METHODS

#### Systematic Review Process: Protocol

The search strategy was implemented according to the population, intervention, comparison, and outcome (PICO) framework (Table 1), based on the following question: Are strontium-coated titanium surfaces more conducive to osseointegration?

#### Table 1. PICO

<table>
<thead>
<tr>
<th>Question</th>
<th>“Are the titanium surfaces, coated with strontium, more osseointegrated?”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Non osteoporotic/osteopenic, rats and rabbits, receiving endosseous implants.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Titanium endosseous implants coated with strontium, in femur and tibia.</td>
</tr>
<tr>
<td>Comparison</td>
<td>Titanium endosseous implants without strontium coating, in femur and tibia.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>BIC, BF%, BA, and BT values.</td>
</tr>
</tbody>
</table>
This assessment involved the modified guidelines provided by ARRIVE (Animal Research: Reporting of In Vivo Experiments), with a total of 22 items. Each item was rated by the reviewers N.L.-V. and J.M.-F. with scores of 0 (not reported) or 1 (reported), with an overall inventory of all the studies included (Table 2).

|------------------------|------------------------|------------------------|------------------------|----------------------|-----------------|------------------|----------------------|-----------------|-----------------|-----------------|-----------------
| 1. Title               | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| Abstract               | 2. Species             | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| 3. Key finding         | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| Introduction           | 4. Background          | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| 5. Reasons for animal models | 1                      | 1                      | 1                      | 0                    | 1               | 1                | 1                    | 0               | 0               | 0               | 0                |
| 6. Objectives          | 7. Ethical statement   | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| Methods                | 8. Study design        | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| 9. Experimental procedures | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| 10. Experimental animals | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| 11. Accommodation and handling of animals | 1                      | 1                      | 1                      | 0                    | 1               | 1                | 0                    | 0               | 0               | 0               | 0                |
| 12. Sample size        | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| 13. Assignment of animals to experimental groups | 1                      | 1                      | 1                      | 0                    | 0               | 0                | 0                    | 0               | 0               | 0               | 0                |
| 14. Anesthesia         | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| 15. Statistical methods | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| Results                | 16. Experimental results | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| 17. Results and estimation | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| Discussion             | 18. Interpretation and scientific implications | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 1               | 1               | 1               | 1                |
| 19. 3Rs reported       | 0                      | 0                      | 0                      | 0                    | 0               | 0                | 0                    | 0               | 0               | 0               | 0                |
| 20. Adverse events     | 0                      | 0                      | 0                      | 0                    | 0               | 0                | 1                    | 0               | 0               | 0               | 0                |
| 21. Study limitations  | 0                      | 0                      | 0                      | 0                    | 1               | 0                | 0                    | 1               | 0               | 0               | 0                |
| 22. Generalization/ applicability | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 0               | 1               | 0               | 0                |
| 23. Funding            | 1                      | 1                      | 1                      | 1                    | 1               | 1                | 1                    | 0               | 1               | 0               | 0                |
| Total score            | 20                     | 20                     | 20                     | 17                   | 20              | 19               | 19                   | 19              | 16              | 16              | 16               |

Each item was judged as “0” (not reported) or “1” (reported). The total score of each of the included studies was also recorded. Mode value: 18.2 ± 2.2.
RESULTS

A total of 255 papers were obtained through November 2018, which were assessed by the reviewers. An initial screening removed six duplicate papers. A second screening removed 232, which left 17 full-text articles for the final selection. Six of these were removed, as they included osteoporotic or osteopenic animals, leaving 11 articles overall for full review.

Regarding the total number of articles finally included (n = 11), they refer to experimental assays involving nonosteopenic animals (Fig 1). Table 3 provides a general description of each study’s experimental details. Figure 2 shows the RoB assessment (SYRCLE RoB) in the studies considered. Most of these studies are not clear about the issues considered regarding randomization, generally presenting a high RoB. In 27.3% of these studies, the assignment of the research groups is suitably blind. Furthermore, in 36.4% of the cases, the animals were chosen at random for the assessment of results, which contrasts with the fact that none of the articles consulted explained whether the animals were accommodated by chance. In turn, in 18% of the papers, the results’ evaluator has acted blind, although in no cases are the data on incomplete results suitably addressed. At least 45.5% of the studies indicate that the study is in some way random.

The ARRIVE criteria in these studies record an average score across the board of 18.2 (± 2.2) out of a maximum of 22. The significance is noted of item 12 (assignment of animals to experimental groups), which is reported in only three of the 11 studies; item 20 (study limitations) in two; item 19 (adverse events) in one; and item 18 (3RsNC replacement, reduction, refinement) was not reported in any of the papers analyzed (Table 2).

In terms of BIC, only one of the 11 studies failed to report on the BIC. Four studies reported the P value, and six reported the standard mean difference (SMD). The strontium-modified implants in all the studies recorded a BIC that was significantly higher than the unmodified ones (P < .001 to P < .05) (Table 4) (Fig 3).

Regarding the improvement in the quality of the implant, BF% was reported in four of the studies. All the authors found significant differences in terms of BF% following strontium-modified implants (Table 4).

In terms of the BA ratio, four papers reported results on the newly formed bone area around the implants, with significant discrepancies across the remaining studies.

Fig 1 Flow diagram.
Experimental studies in animals. Fig 2

Table 3: Experimental Details of Each Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Animal model and number</th>
<th>Location of implant placement</th>
<th>Surface preparation method</th>
<th>Tracing (wk)</th>
<th>Analysis methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offermanns et al (2018)</td>
<td>Acta Biomater</td>
<td>Rabbit (36)</td>
<td>Distal part of femur</td>
<td>Magnetron sputtering process</td>
<td>2 wk group 1</td>
<td>Histomorphometry</td>
<td>BIC BF%</td>
</tr>
<tr>
<td>Huanhuan et al (2017)</td>
<td>J Biomater Appl</td>
<td>Rat (20)</td>
<td>Proximal tibiae</td>
<td>Magnetron sputtering process</td>
<td>2 wk group 1</td>
<td>Histomorphometry</td>
<td>RTT BIC BA</td>
</tr>
<tr>
<td>Li et al (2015)</td>
<td>Int J Nanomedicine</td>
<td>Rat (40)</td>
<td>Distal part of the femur</td>
<td>Magnetron sputtering process</td>
<td>12 wk</td>
<td>Histomorphometry SEM Micro-CT</td>
<td>BIC MAR BPT</td>
</tr>
</tbody>
</table>

BIC = bone-to-implant contact; BF% = bone formation; BA = bone area; SEM = scanning electron microscopy; RTT = removal torque test; BV = bone volume; BSA = bone surface area; MAR = mineral apposition ratio; BPT = biomechanical pull-out test; RFA = resonance frequency analysis; ISQ = implant stability quotient.

SYRCLE’s tool for assessing risk of bias

Q1: Was the allocation sequence adequately generated and applied?
Q2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?
Q3: Was the allocation adequately concealed?
Q4: Were the animals randomly housed during this experiment?
Q5: Were the caregivers and/or investigators blinded from knowledge of which intervention each animal received during the experiment?
Q6: Were the animals selected at random for outcome assessment?
Q7: Was the outcome assessor blinded?
Q8: Were incomplete outcome data adequately addressed?
Q9: Are reports of the study free of selective outcome reporting?
Q10: Was the study apparently free of other problems that could result in a high risk of bias?

Fig 2: Risk of bias evaluated using the SYRCLE RoB tool (Systematic Review Center for Laboratory Animal Experimentation), for experimental studies in animals.

The results in all four cases. Park et al did not find any significant differences between titanium and titanium+strontium implants (46.7 ± 10.7 vs 46.6 ± 6.5, P > .01). Fan et al analyzed two groups of SLA with and without a strontium coating; they did not report any results for the first group (21 days), and in the second case (42 days), they reported a lower BA for the SLA+strontium group (0.80 ± 1.65 SLA+strontium vs 6.34 ± 6.51 SLA+titanium, P < .05). Park et al concluded that there are no significant differences in terms of...
BA between implants with an SLA surface and those with SLA+strontium (57.3 ± 9.4 vs 60.9 ± 10, P = .386). By contrast, Huanhuan et al reported a significant difference in BA between SLA surfaces and those with SLA+strontium (29.55 ± 5.53 vs 41.62 ± 7.75, P < .05).

Only one of the studies analyzed reported a significant reduction in BA with strontium-coated implants in spongy bone (Table 4).

Regarding the BT, five of the studies evaluated the biomechanical removal tests, both the removal torque test and the biomechanical pull-out test, reporting a significant increase in the force required to extract the strontium-treated implants (Table 4).

**DISCUSSION**

In order to select the articles, the Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) were followed. The PRISMA approach is the best way to find the studies related to the topic of interest.
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Although the literature contains rigorous reviews of the osseointegration effect of strontium-coated titanium, the authors of the present study understand that, to the best of their knowledge, this article is the first literature review to assess the effect of strontium-modified titanium surfaces in vivo experimental assays involving healthy, nonosteoporotic and/or non-osteopenic animals.

Different studies have shown that strontium-containing biomaterials could increase bone apposition. Studies assessing bioactive scaffolds that incorporate strontium into certain cements used on damaged bone have found that strontium-modified materials are covered by more newly formed bone than those that are unmodified.

Although different methods have been described for coating titanium surfaces with strontium, the studies selected here have used only two coating processes, namely, the magnetron sputtering process and hydrothermal treatment (Table 3). Nevertheless, the coating method does not appear to have an influence on the BIC percentage.

Most of the studies used here have a high RoB, according to the corresponding analysis (Fig 2), although all the papers conclude that strontium-coated titanium surfaces have a greater capacity for osseointegration.

Although four parameters have been evaluated here (BIC, BF%, BA, and BT), the main focus has been on BIC as the most predictive way of measuring an implant’s osseointegration. The outcome is that strontium-coated titanium implants record BIC percentages that are significantly higher than those that have not been modified with strontium.

Regarding the experimental animal, seven of the studies analyzed involved rabbits and four rats and five provide data on biomechanical properties. It should be noted that not one of them reports on all four parameters.

The authors therefore consider that the quality of the reports in terms of preclinical studies should be improved in certain areas, such as statistical data, the design and configuration of the studies, and their possible extrapolation to human beings.

Clinical tests and randomized controlled clinical trials are required to endorse the use of strontium as a coating for titanium implants for osteoinduction purposes, and thereby provide surfaces that ensure rapid osseointegration.

Table 4 BIC, BF%, BA, and BT Values

<table>
<thead>
<tr>
<th>Tracing (days)</th>
<th>Ti</th>
<th>Ti-Sr</th>
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CONCLUSIONS

Nine of 11 studies reported that titanium implants coated with strontium showed significantly higher BIC ($P < .001$ to $P < .05$). This coating also improved the implants’ biomechanical properties.

ACKNOWLEDGMENTS

The authors have declared that no conflicts of interest exist.
REFERENCES


