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Does strontium coated titanium implants enhance the osseointegration in animal models under osteoporotic condition? A systematic review and meta-analysis

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PURPOSE: The aim of this study was to systematically review the literature to address the effect of strontium modified titanium implants on the osseointegration in the presence of osteoporotic conditions through animal models.

MATERIALS AND METHODS: The databases (PubMed, Scopus, Web of Science, and EBSCO) were searched electronically, and manual searches were performed till December 2022 to identify preclinical studies on the osseointegration of strontium coated titanium implants in animals with induced osteoporotic conditions. The primary outcomes were the bone-implant contact percentage (BIC%), bone area (BA) from the histomorphometric analysis, and the osseointegration parameters from biomechanical tests; the secondary outcomes were the osseointegration parameters from the micro computed tomography.

RESULTS: Nineteen articles were included for the quantitative analysis on basis of the inclusion criteria. The results revealed that Sr-modified implants showed a significant 19.05% increase in BIC, and 15.01% increase in BA. The results of biomechanical tests indicated a significant effect in favor of Sr-coated implants. Furthermore, Results of the secondary outcomes supported the significant advantages of Sr-coated implants over the un-coated implants. The overall, systematic analysis of implants osseointegration parameters proved a significant increase in favor of Sr-coated titanium implants ($P < 0.01$).

CONCLUSION: The present results provide evidence that strontium-coated titanium implants enhanced the osseointegration in animal models under osteoporotic condition as this surface modification techniques have improved the mechanical and biological properties of the titanium implants.

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INTRODUCTION

Dental implants have become the most effective and predictable means of teeth replacement for both partially and totally edentulous patients due to their high success and survival rates [1]. This success depends on achieving and maintaining a direct structural and functional connection between ordered living bone and the surface of load carrying implant in a process known as osseointegration. According to Albrektsson et al., Implant material biocompatibility, implant surface, implant design, surgical and loading techniques, and host tissue condition are the main six factors that influence osseointegration [2].

In spite of all advancements in the field of dental implantology, there still exist a significant population of patients where dental implant treatment is considered as a relative contraindication due to the unpredictable outcomes where there is no consensus in the literature regarding the success and survival rates of dental implants in these patients. These relative contraindications include any medical conditions that affect bone metabolism or the patient's ability to heal, such as diabetes, osteoporosis, immune

compromise conditions, and medical treatments such as chemotherapy [3–5].

Osteoporosis is a generalized skeletal disorder characterized by reduction in bone density and deterioration of the microarchitecture of the bone tissue due to high bone turnover rates and imbalance in bone remodeling, where bone resorption exceeds bone formation, leading to bone fragility with greater risk of bone fracture and decreased capacity of bone to repair [6, 7]. Several previous experimental studies have reported the negative effect of osteoporosis on the extraction socket healing [7], as well as on the osseointegration of dental implants [8–10].

The aging population of humans are progressively increasing, so more people will be affected by osteoporosis and missing teeth, so it is expected that the number of osteoporotic patients who are in need to replace their missing teeth by dental implants will increase all over the world [11]. Thus, it is essential to develop a scientifically validated technologies to improve implant osseointegration in such conditions to achieve more predictable outcomes.

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Currently, the majority of implant systems available in the market are using the well-established sandblasting acid etching (SLA) technique as a standard surface treatment modality to greatly improve the roughness, hydrophilicity, cell adhesion, and consequently the bone-implant integration [12]. Nevertheless, in some challenging bone situations, such as low bone quality and quantity, the SLA surface lacks sufficient pro-osteogenic bioactivity to induce adequate osteogenesis to ensure successful implant osseointegration [13]. Therefore, to promote the mechanical and biological performance of titanium implants, a surface modification with co-osteogenic properties is highly recommended to enhance the osseointegration and achieve a more predictable outcomes in such challenging bone conditions.

Srontium (Sr) is an essential microelement in the human body that, like calcium, has powerful bone-seeking characteristics. It is currently used in the treatment of osteoporosis [14]. In contrast to the anticatabolic drugs like bisphosphonates that decrease bone resorption, and the anabolic drugs like parathyroid hormone that enhance bone deposition, Sr has a unique dual mechanism of action as it is simultaneously induce bone formation through increasing the osteoblastic activities and at the same time prevent bone resorption through reduction of osteoclastic activities. This dual action has been reported in several previous *in vitro* experiments [15, 16]. Furthermore, several previous *in vivo* studies, performed in both normal and osteoporotic animal models, showed that Sr-coated titanium implants have significantly better osseointegration parameters than Sr-free implants [17–19].

Two previous systematic reviews have proved the positive effect of Sr-coated titanium implants on the osseointegration in healthy, non-osteoporotic conditions [20, 21]. Furthermore, a prior systematic review has demonstrated the beneficial effect of strontium supplementation on implant osseointegration in osteoporotic settings [22]. However, the efficacy of Sr coated titanium implants on improving new bone formation and enhancing implant osseointegration in the presence of osteoporotic conditions is still unclear. Therefore, the aim of this study was to systematically review the effect of Sr modified titanium implants on the osseointegration in the presence of osteoporotic conditions through animal models.

METHODS

This systematic review and meta-analysis follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards and adheres to the guidelines from the Cochrane Handbook [23, 24].

PICO question

To answer the research question: "Does strontium coated titanium implants enhance the osseointegration in animal models under osteoporotic condition?", the Population, Intervention, Control, and Outcomes (PICO) approach was applied (Table 1). The Population was animals with induced osteoporotic conditions received endosseous implants; the Intervention was Strontium-coated titanium implants; the Comparator was titanium implants without strontium coating; the primary outcomes were the bone-implant contact percentage (BIC%) and the bone area (BA) mainly from the histomorphometric analysis, and the osseointegration parameters from biomechanical tests; the secondary outcomes were the osseointegration parameters from the micro computed tomography.

Eligibility criteria

The inclusion criteria that were applied were as follows: [1] *in-vivo* models with induced osteoporosis; [2] preclinical studies that provide any quantitative data for the primary or secondary outcomes mentioned above.

Table 1. PICO.

PICO	
Question	Does strontium-coated titanium implant enhance the osseointegration in animal models with osteoporotic conditions?
Participants	Osteoporotic animal models receiving endosseous implants.
Intervention	Titanium endosseous implants coated with strontium.
Comparison	Titanium endosseous implants without strontium coating.
Primary Outcomes	<i>Histomorphometric analysis:</i> Bone-implant contact percentage BIC% <i>Biomechanical tests:</i> Removal torque (N.cm) Max. pull out force (N) Max. push out force (N) Push-in force (N)
Secondary outcomes	<i>Micro-CT osseointegration parameters:</i> Bone volume/Total volume Bv/Tv. Trabecular bone Thickness Tb.Th (micro m) Trabecular Separation Tb.Sp (micro m) Trabecular number Tb.N (1/mm) Connectivity Density Conn.D

The following exclusion criteria were applied: [1] All secondary works, such as meta-analyses and reviews; [2] *in vitro* studies; [3] studies that address the hybrid effect of Sr and other elements; [4] non-osteoporotic animal studies; [5] studies with systemic administration of Osseo-inductive drugs.

Search strategy and study selection

A comprehensive search was conducted, including the databases MEDLINE via PubMed, Web of Science, Scopus, and EBSCO, until December 2022 for articles that matched the inclusion criteria without language restrictions. The following keywords were used as search terms in PubMed: [("strontium" OR "Sr" OR "Strontium[Mesh] OR Strontium-incorporated OR Strontium-surface OR strontium-coat OR strontium-coating OR strontium-oxide OR Sr-coat OR Sr-HA OR NT-Sr OR nano-Sr OR nano-strontium OR strontium-substituted OR strontium-functionalized OR strontium-loaded OR Strontium-modified OR Sr-modification OR SLA-Sr) AND (titanium OR Ti OR implant OR implantation OR implants OR SLA OR "Titanium[Mesh]" OR "Dental Implants[Mesh]") AND ("osteoporosis OR osteoporotic OR osteopenia OR osteopenic)]. (The comprehensive search strategies for all databases are provided in supplementary data).

The included articles were screened in three steps. The first step implied importing the results from electronic databases to a Microsoft Excel sheet using EndNote Software (*EndNote 20, Clarivate: Philadelphia, PA*). The second step was done by two independent authors and included title and abstract screening of the articles imported to the Excel sheet. The third step was the full-text screening of the included citations from step 2. Additionally, the references of the included articles were manually searched for possible missed studies.

Data collection

Two independent reviewers separately collected three categories of data from each included study: the first category is the baseline and characteristics of the included subjects, such as the author, year, sample size, animal model, sex, age, Sr integration methods onto the implant coating, Sr concentration, implant size and design, the implantation site and follow-up periods. The second

category included the outcomes of analysis, mainly: BIC, BA and biomechanical tests. Plot digitizer 2.6.9 (<https://plotdigitizer.com>) was used to compute the quantitative values expressed only in graphs. The third category included data for risk of bias assessment. The process of data collection was done using Microsoft Excel.

Risk of bias assessment and quality of reports

The risk of bias tool provided by SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) [25] was used to assess the reported methodology of the included studies. Two authors assessed the risk of bias among included studies. The tool assesses proper randomization, allocation concealment, adequate blinding, and outcome reporting through nine domains. Each domain is put to either "low", "unclear", or "high" risk of bias. For the quality of reports, the modified ARRIVE guidelines (Animal Research: Reporting of In Vivo Experiments) [26] were applied. Two reviewers assigned a score of 0 (not reported) or 1 (reported) to each item out of 23 items, then the overall score of each study was evaluated.

Analysis

The meta-analysis of this study was performed using Review Manager Software (*RevMan 2020, The Cochrane Collaboration*). The study included continuous outcomes which were analyzed using mean difference (MD) for BIC, BA, bone architecture parameters from the Micro-CT, and standard mean difference (SMD) for biomechanical tests with a 95% confidence interval (CI). A random-effect model was used due to the substantial heterogeneity. To measure the presence of inconsistency among the studies, the I^2 and the p -value of the Chi-square tests [24] were used. Values of $P < 0.1$ or $I^2 > 50\%$ were significant indicators of the presence of heterogeneity. Sensitivity analysis was used in a trial to solve the inconsistency of heterogeneous outcomes. Finally, Forest plots to visualize the estimated effect sizes and funnel plots to identify publication bias were generated if 10 or more studies were included.

RESULTS

Results of literature search

The study screening process is summarized in Fig. 1. The electronic search yielded a total of 1183 records while the manual search identified 7 records of relevance. After duplicate removal, a subsequent title and abstract screening of the 911 articles concluded that 42 articles were eligible for inclusion. The full texts were then assessed, and 19 articles were included for the qualitative and quantitative synthesis on basis of the inclusion criteria. (Full-text excluded studies are presented in the supplementary data).

Characteristics of included studies

Table 2, summarizes the general characteristics of the included studies. In summary, nineteen studies were included in the systematic review to investigate the effect of strontium surface coating on implant osseointegration in animal with induced osteoporosis [17, 27–44]. The majority of investigators used rodents, as fifteen research utilized rats, three studies used rabbits, and one study used sheep. Eleven studies used the femur for implantation, six studies used the tibia, one study used both the tibia and the femur, and one study used the mandibular angle. The overall follow-up periods ranged from 2 to 12 weeks.

The implant characteristics in the included studies were as follows; a total of 506 implants were used. In terms of implant design; 9 studies used rod-shaped implants, 9 studies utilized screw-shaped implants, and one study used wire-shaped implants, the implant diameter ranged from 0.8 to 4.3 mm and the implant length ranged from 4 to 20 mm.

Results of risk of bias and quality of reports assessment

SYRCLE risk of bias assessment tool results are shown in Fig. 2. The ARRIVE criteria of the included studies recorded an average score across the board of $19.15(\pm 1.46)$ out of a maximum of 23. All the included studies reported correctly on the title, abstract, introduction, ethical statement, species, surgical procedure, outcomes assessment, and statistical analysis. On the other hand,

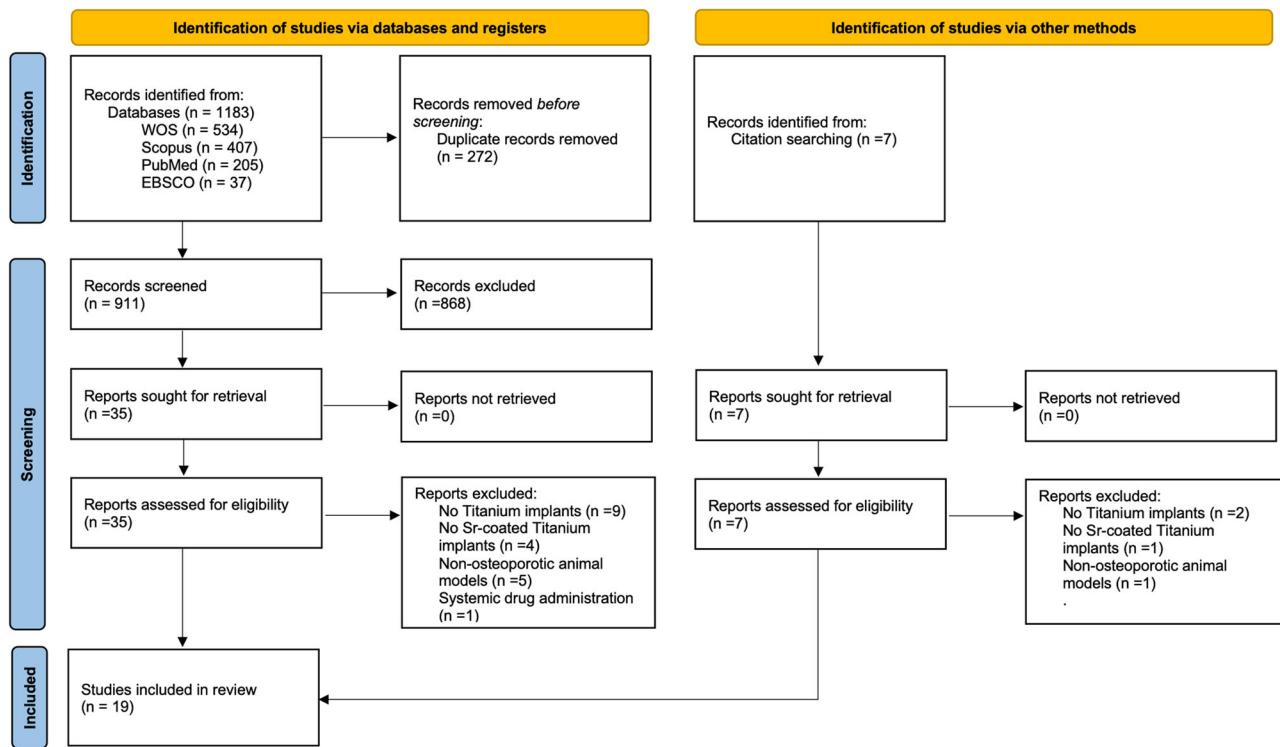


Fig. 1 PRISMA Flowchart for the process of study selection.

Table 2. Characteristics of the included studies.

Study	Subject model, sex & age	Intervention groups	Follow-up periods	Sr integration methods	Assessment methods	Outcomes
Geng [27]	Female New Zealand white rabbits, 1 Y	Ti, Ti-Ca3.7, Ti-Ca4.9, Ti-Sr3.7 and Ti-Sr4.9 (The numbers indicate pH value of preparation)	1, 2, 3 m	Electrochemical deposition	micro-CT, Histological analysis, biomechanical push-in test.	Tb.Th, (BIC), push-in force.
Katunar [28]	Female Sprague Dawley rats	Ti implants, Ti BG, and Ti BG Sr	15 & 30 d	Sol-gel technique	Micro-Raman spectroscopy maps and histomorphometric analysis.	BA, Tb.Th.
Li [30]	Female Sprague Dawley rats, 6 m	Hybrid micro/nanorough titanium strontium-loaded (MNT-Sr) surface, smooth titanium surface (ST), microrough titanium surface (MT) and strontium-loaded nano titanium NT-Sr	12 w	Magnetron sputtering	Micro-CT scanning, Histological analysis, pull-out test	Tb.Th, Tb.N, Tb.Sp, BV/TV, BIC, maximum pull-out force
Li [29]	Female Sprague Dawley rats, 3 m	HA-coated implants and 10% SrHA coated implants	12 w	Solgel technique	Histomorphometry, micro-CT evaluation and the maximal push-out force	BIC, BA, BV/TV, Tb.Th, Tb.N, Tb.Sp, Conn.D, and maximal push-out force
Li [30]	Female Sprague Dawley rats, 3 m	HA-coated implants and 10% SrHA coated implants	8 w	Chemical coprecipitation	Micro-CT assessment and Histomorphometry;	BIC, BV/TV, Tb.N, Tb.Th, Conn.D and Tb.Sp
Liang [31]	Female Sprague Dawley rats, 3 m	Implants with a Sr coating and implants without an Sr coating	4 w	Electrochemical deposition	Histomorphometry, Fluorescent histology, Biomechanical testing	BIC, BV/TV, removal torque
Lin [32]	Female New Zealand rabbits, 6 m	SHAM-SLA-Sr, OVX-SLA-Sr, SHAM-SLA and OVX-SLA.	3 & 6 w	Hydrothermal treatment	Removal torque test and histomorphometric analysis	removal torque values, BIC%, BA%
Liu [33]	Female sheep 4 ± 0.7 y	Hybrid micro/nanorough titanium strontium-loaded (MNT-Sr) surface, smooth titanium surface (ST), microrough titanium surface (MT) and strontium-loaded nano titanium NT-Sr	12 w	Magnetron sputtering	Micro-CT, Histomorphometry, Pull out test;	BV/TV, Tb.Sp, Tb.Th, BIC, the maximum pull-out force
Mi [34]	Female Sprague Dawley rats, 10 weeks	Sham, OVX, OVX + Ti, OVX + TiO2-NTs, OVX + NT-Sr1h, and OVX + NT-Sr3h	8 w	Hydrothermal treatment	Micro-CT, Histological analysis and Serum analysis.	BV/TV, Tb.Sp, Tb.Th, Tb.N.
Offermanns [35]	Female Wistar rats	Unmodified Ti implants; Ti-Sr-O (22 minites-wash); Ti-Sr-O (no wash); Ti-Sr-O (industrial wash).	6 & 12 w	Magnetron sputtering	Histomorphometry.	BIC, BA
Shen [36]	Female Sprague Dawley rats	Normal [Sr25% (n = 5) & Sr1000% (n = 5)] and osteoporotic groups [Ti & Sr100% (n = 10), Sr25% (n = 10) & Sr100% (n = 10)].	6 & 7 d, 1 m	Micro-arc oxidation (MAO)	Micro-CT, Histomorphometry, Oxidative stress level and Macrophage polarization	BV/TV, Tb.N, Tb.Th, Tb.Sp
Tao [37]	Female Sprague Dawley rats, 3 m	HA, 5% Sr-HA, 10% Sr-HA, and 20% Sr-HA	12 w	Electrochemical deposition	Histological, micro-CT, and pushout tests	BV/TV, Tb.Th, Tb.N, Tb.Sp, Conn.D, Max. push out force, BIC and BA

Table 2. continued

Study	Subject model, sex & age	Intervention groups	Follow-up periods	Sr integration methods	Assessment methods	Outcomes
Tao [38]	Female Sprague Dawley rats, 3 m	HA, 10% Zn-HA, 10% Mg-HA and 10% Sr-HA	12 w	Electrochemical deposition	Histological, micro-CT, and pushout tests	BV/TV, Tb.Th, Tb.N, Tb.Sp, Conn.D, Max. push out force, BIC and BA
Tao [39]	Female Sprague Dawley rats, 3 m	HA, 10% Sr-HA group, PTH group and PTH+Sr group	12 w	Electrochemical deposition	Histological, micro-CT, and pushout tests.	BV/TV, Tb.Th, Tb.N, Tb.Sp, Conn.D, Max. push out force, BIC and BA
Wang [40]	Female Sprague Dawley rats	AH-Ti and AH-Ti/Sr90 (deposition durations 90 min)	4 w	Magnetron sputtering	Micro-CT and histological analysis.	BV/TV, Tb.Th, Conn.D.
Wen [41]	Female Sprague-Dawley rats, 3 m	(i) Ti group ($n = 8$); (ii) TiO ₂ group ($n = 8$); (iii) AT-TiO ₂ group ($n = 8$); (iv) Sr-TiO ₂ group ($n = 8$).	8 w	Micro-arc oxidation	Sequential fluorescent labeling and Histomorphometric analysis	BIC
Zhang [42]	Female Sprague Dawley rats, 3 m	HA, 2.5% Zn-HA, 2.5% Mg-HA, and 2.5% Sr-HA	4, 8, 12 w	Electrochemical deposition	Histomorphometric Analysis	BIC, BA
Zhao [43]	Female New Zealand rabbits, 5–6 m	A: machined surface, B: MAO and C: MAO-Sr-simvastatin	4, 8, 12 w	Micro-arc oxidation (MAO)	Pull-Out Tests, Histomorphometric analysis	Maximum pull-out force, BIC
Zhu [44]	Female Sprague Dawley rats, 12 weeks	Sham+Ti, Ti, TiO ₂ , TiO ₂ +Sr and TiO ₂ +Sr+ICA.	4 w	Hydrothermal treatment	Micro-CT assessment and Histomorphometry.	BV/TV, BIC

Sr strontium, HA hydroxyapatite, Ti titanium, SLA sandblasted acid-etched, Micro-CT microcomputed tomography, BIC bone to implant contact, BA bone area, MAO micro-arc oxidation, RTT removal torque test, BV/TV bone volume/total volume, Tb.Sp trabecular spacing, Tb.N trabecular number, Tb.Th trabecular thickness, Conn.D the mean connective density.

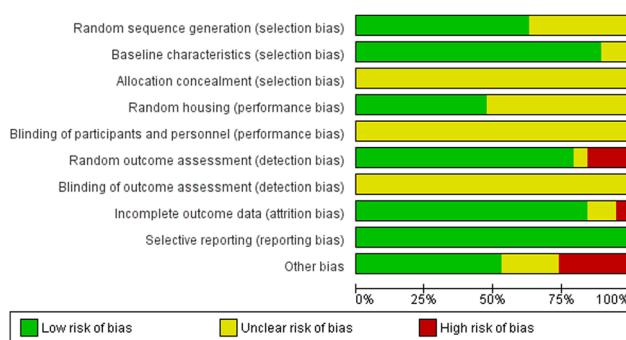


Fig. 2 Risk of bias (RoB) evaluation by the Systematic Review Centre for Laboratory animal Experimentation (SYRACLE) RoB assessment tool.

none of the included studies reported 3Rs or the presence of adverse events (Table 3).

Analysis of outcomes

To assess the implant osseointegration in test subjects with osteoporosis the included studies used histological, radiographical, as well as biomechanical analysis. Histological and radiographical analysis were used mainly to evaluate the bone implant contact (BIC), bone area (BA), and bone microstructure parameters: Bone volume / Total volume BV/TV, Trabecular Thickness Tb.Th (micro m), Trabecular Separation Tb.Sp (micro m), Trabecular number Tb.N (1/mm), Connectivity Density Conn.D. Moreover, different biomechanical tests were used including removal torque test, maximum pull out test, maximum push out test and maximum push-in test. The overall, systematic analysis of implants osseointegration parameters proved a significant increase in favor of Sr-coated titanium implants.

Histomorphometric parameters assessment

Regarding the primary outcomes, the BIC pooled analysis of the 15 included studies showed a statistically significant superior results in favor of Sr coated implants with 19.05% increase ($P < 0.00001$) despite considerable heterogeneity ($\chi^2 = 485.41$, ($P < 0.00001$), $I^2 = 97\%$) (Fig. 3). Subgroup analysis according to the animal model, implantation location, and follow-up period could not explain the source of heterogeneity neither did the sensitivity analysis. Furthermore, the funnel plot illustrated the presence of publication bias (Fig. 4).

The Bone Area (BA) $n = 9$ studies significantly increased in Sr-coated group (15.01%, $P < 0.00001$) with considerable heterogeneity ($I^2 = 75\%$), the sensitivity test by excluding one study resulted in homogenous results in favor of Sr-coated implants ($P = 0.31$); $I^2 = 16\%$) (Fig. 5).

Results of the secondary outcomes supported the advantages of Sr-coated implants, Bone volume per total volume (BV/TV) ($n = 11$ studies) was significantly higher in the Sr-coated group (MD = 12.48%, $P < 0.00001$); likewise, connectivity density (Conn.D) ($n = 6$ studies) was also better in the Sr-coated group (MD = -15.16 mm^{-3} , $P = 0.0004$). Trabecular thickness (Tb.Th) $n = 12$ studies showed overall significant increase in Sr-coated group (21.11 mm^{-3} , $P < 0.00001$), trabecular number (Tb.N) $n = 8$ as well increased significantly ($27.64 (1/\text{mm})$, $P < 0.00001$), and trabecular spacing (Tb.Sp) $n = 9$ studies significantly favored Sr-coated group (-151.02 mm^{-3} , $P < 0.00001$). Considerable heterogeneity was observed in all the present secondary analyses (I^2 ranged from 88% to 100%). To sum up, the analyzed studies displayed higher BV/TV, Conn.D, Tb. N, and Tb.Th, along with reduced Tb.Sp in the Sr-coated group.

Biomechanical testing

The meta-synthesis of biomechanical tests included 10 studies of which four studies used maximum push-out test, three studies

used maximum pull-out test, two studies used removal torque and one study used maximum push-in test. The overall SMD is 2.05 ($P < 0.00001$) which indicates a large effect in favor of Sr-coated implants according to Cohen's rules of thumb [45], however the overall analysis resulted in moderate heterogeneity ($(P = 0.02)$; $I^2 = 56\%$). The sensitivity analysis showed that two studies were responsible for the heterogeneity, excluding both studies resulted in homogenous results in favor of Sr-coated implants ($P = 0.31$); $I^2 = 15\%$) (Fig. 6).

DISCUSSION

Continuous advancements in dental implant material, design, surface treatment, as well as developments in surgical techniques, have not only shortened treatment time but also expanded the indications for implant therapy where a larger population of patients are now candidates for implant therapy. As a result, there is a growing interest in patients who have disease-related factors that may impact implant integration and success.

Osteoporosis is a systemic bone metabolic disease that affect implant osseointegration and therefore is considered as a potential risk factors for implant failure [46, 47]. Hence, the development of new therapeutic approaches should consider these physiologic determinants. The included studies compared the osseointegration of Sr coated titanium implants in simulated osteoporotic animal models versus Sr free implants.

Findings of this systematic review demonstrate the catalytic influence of Sr-modified implant surfaces in implant osseointegration in osteoporotic conditions based on the results of histomorphometric, microcomputed, and biomechanical analysis for the implant-bone samples. Moreover, the meta-analysis of the primary outcomes (BIC, biomechanical tests) supports the significant increase in the percentage of BIC and biomechanical test values in favor of Sr-modified implant surfaces.

This systematic review aimed to investigate the effect of Sr-modified implant surfaces on enhancing osseointegration and bone apposition in animals with metabolic osteoporotic conditions, in addition, a meta-analysis was performed to quantify the potential effect of Sr-coated surfaces on peri-implant bone apposition in terms of BIC, biomechanical integration and trabecular bone architecture.

Recently wide range of strontium compounds emerged in treating bone defects through systemic administration of drugs such as Sr ranelate or direct delivery of local agents such as injectable Sr-HA containing bioactive bone cement and Sr-doped ceramics to accelerate the bone healing process. However, Sr delivered systemically does not reach high enough concentrations inside the bone to produce a significant biological stimulation of bone formation [48]. Moreover, it poses serious side effects as increased incidence of venous thromboembolism (VTE), non-fatal myocardial infarction [49] and recently it has been contraindicated in patients with uncontrolled hypertension, ischemic heart disease, peripheral arterial disease, and/or cerebrovascular disease [50]. On the other hand, local delivery of strontium compounds resulted in enhanced bone growth and osseointegration at the bone-implant interface [42, 51]. Furthermore, Offermanns et al. have utilized the Atomic Absorption Spectrometry (AAS) to measure the serum levels of strontium to address any potential systemic effect of the released strontium from the titanium surface [18]. These authors reported that spectrometry measurements did not indicate any potential systemic effect by the local release of strontium from the implant surface [18]. Thus, the main concern to boost implant bone integration should be directed towards Sr-modified implant surfaces, especially in cases where bone quality is questionable.

Interestingly, all the included studies attributed the enhanced implant osseointegration and bone architecture to the local leaching of Sr ions. Strontium has a dual action aims to overcome

Table 3. ARRIVE criteria reported by the included studies.

ARRIVE	Geng [27]	Katuniar [28]	Li [30]	Li [29]	Li [30]	Liang [31]	Lin [32]	Liu [33]	Mi [34]	Offermanns [35]	Shen [36]	Tao [37]	Tao [38]	Wang [40]	Wang [39]	Wen [41]	Zhang [42]	Zhang [43]	Zhu [44]
1.Title	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abstract																			
2.Species	0	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1
3.Key finding	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Introduction																			
4.Background	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5.Reasons for animal models	0	1	0	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	1
6.Objectives	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Methods																			
7.Ethical statement	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
8.Study design	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
9.Experimental procedures	1	1	1	1	1	1	1	1	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	1	1	1	1	1	1	1	1
11.Accommodation and handling of animals	0	0	1	0	1	0	1	1	0	1	0	1	1	1	0	0	0	0	1
12.Sample size	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
13.Assignment of animals to experimental groups	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
14.Anaesthesia	1	1	1	0	0	1	1	1	1	1	0	1	1	0	0	0	0	1	1
15.Statistical methods	1	1	1	1	1	1	1	1	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	1	1	1	1	1	1	1	1	1
17.Results and estimation	1	1	1	1	1	1	1	1	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	1	1	1	1	1	1	1	1	1
19.RRs reported	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20.Adverse events	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21.Study limitations	0	1	1	0	1	0	1	0	1	0	1	1	1	0	1	1	0	0	0
22.Generalization/ applicability	1	1	0	1	1	1	1	1	1	1	1	0	0	1	1	1	0	1	1
23.Funding	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Total score	16	20	18	20	20	19	21	20	20	21	17	20	19	20	17	19	20	17	20

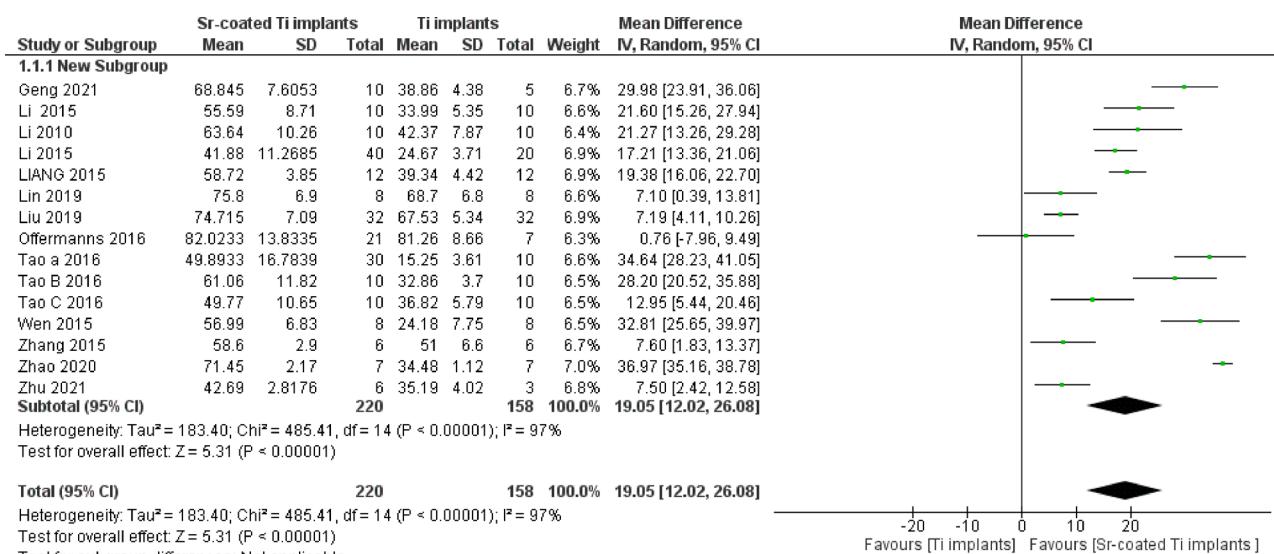


Fig. 3 Bone to implant contact (BIC) forest plot.

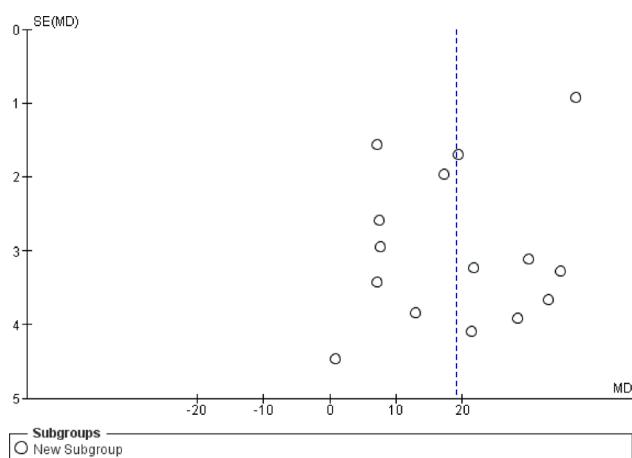


Fig. 4 Bone to implant contact (BIC) funnel plot.

the accelerated bone loss associated with osteoporosis by rebalancing bone remodeling in favor of bone formation through a calcium-sensing receptor (CaR)-mediated mechanism, on one hand Sr increases bone apposition by promoting pre-osteoblastic cell differentiation and inducing osteoblast survival and proliferation through the Canonical Wnt Signaling (Wnt/β-Catenin Pathway) [52], on the other hand, Sr directly induces osteoclast apoptosis through a signaling pathway dependent on the activation of diacylglycerol (DAG)-protein kinase C (PKC) β II [53], and indirectly reduces osteoclast development and activity by increasing the expression of osteoprotegerin (OPG) and decreasing the expression of receptor activator of nuclear factor κ B ligand (RANKL) [54]. In addition, Sr coated implants have increased surface roughness that promotes osteoinductive cells attachment to the implant surface which works in tandem with the released Sr ions to improve implant osseointegration [21].

In the current study, consistent results were obtained from the histomorphometric, biomechanical and micro-CT evaluation techniques. All the analyzed osseointegration parameters showed positive results in favor of Sr-incorporated implants. Such consistency in results were in agreement with those of previous reviews that address the effect of Sr coated titanium implants on the osseointegration in healthy, non-osteoporotic conditions [20, 21], and were in agreement with previous preclinical animal

studies of Sr- incorporated bioactive glass scaffolds and bone cement containing biomaterials [55, 56].

In this study, the primary outcome variables were the BIC% and bone area (BA) recorded by the histomorphometric analysis, and the biomechanical tests. Results of the histomorphometric assessment were prioritized over microcomputed tomography (μCT) when both approaches were used to assess the same outcome, and this preference was in agreement with Zhou et al. and Zhu Y et al. [44, 57], as it provides the most precise method of recording morphological changes at the implant-bone interface [58], and it is considered the most accurate way to assess implant osseointegration [59]. All the included studies that investigated BIC % reported significant results in favor of Sr-coating, and this was solidified by the meta-analysis. Moreover, the bone area (BA) was analyzed to evaluate the quality and quantity of peri-implant bone apposition as it reflects the new mineralized bone tissue area inside all implant threads and plays an important role in assessing the osteoconductive property of biomaterials. Eight included studies have evaluated the bone area, all of them reported significant improvement for Sr modified implant surfaces compared to Sr free implant surfaces. In addition, biomechanical tests were analyzed, as these tests are sensitive to changes in the mechanical properties of the bone-implant interface to predict its stability against various applied forces as healing progress [59]. Sr coated implants showed a significant increase in implant fixation compared to Sr-free implants.

For the secondary outcomes, the micro-computed tomography analysis was performed as it provide a nondestructive and a comprehensive evaluation of the trabecular architecture of peri-implant bone tissue [60]. Bone microstructure parameters (BV/TV, Tb.Th, Tb.N, Tb.Sp and Conn.D) were analyzed to evaluate the quality and quantity of peri-implant bone apposition, and all the included studies showed significant bone architecture enhancement in favor of Sr-coated implants.

The selected studies in this systematic review have reported using various surface coating methods to incorporate Sr ions on implant surface; six studies used electrochemical deposition, four studies used magnetron sputtering, three studies used hydro-thermal treatment, three studies used micro-arc oxidation (MAO), two studies used sol-gel technique, and one study used chemical coprecipitation, however coating methods didn't have any significant influence in the BIC%. Such results were consistent with findings obtained by López-Valverde et al. [21].

The present meta-analysis shows considerable heterogeneity, this disparity could be due to the different surface topography, Sr

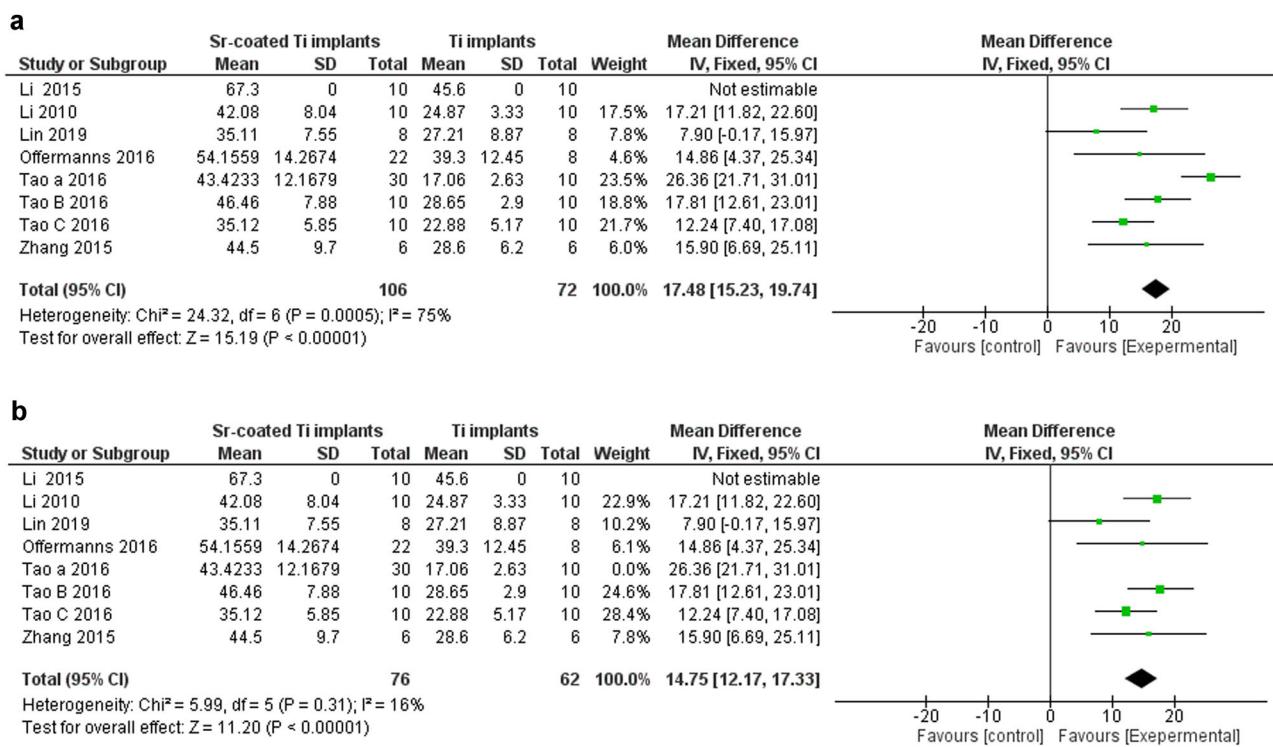


Fig. 5 Bone area (BA) forest plot sensitivity analysis. **a** BA forest plot. **b** BA forest plot after excluding the sources of heterogeneity and performing sub-group analysis.

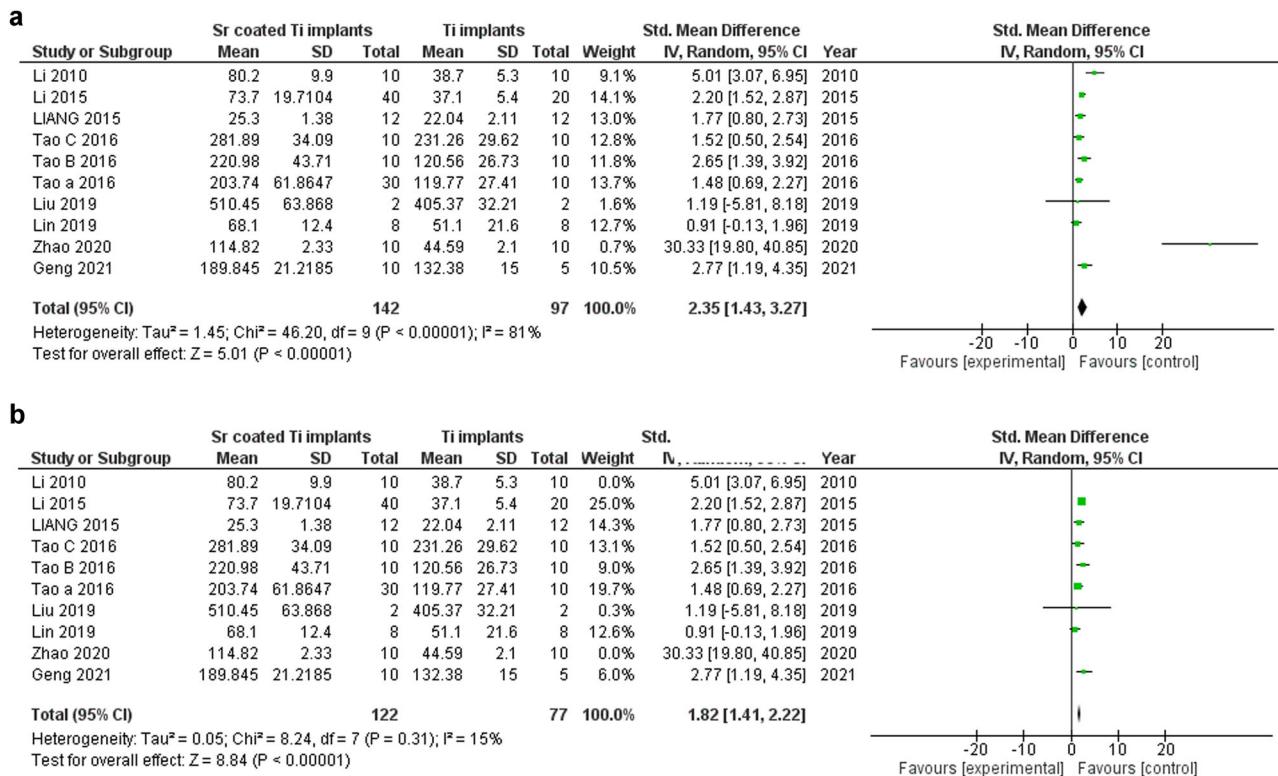


Fig. 6 Biomechanical tests forest plots sensitivity analysis. **a** Biomechanical tests forest plots. **b** Biomechanical tests forest plots after excluding the sources of heterogeneity and performing sub-group analysis.

concentration in titanium implant surfaces, the different methods for incorporating Sr into implant surfaces, and follow-up periods, furthermore, subgroup analysis based on animal type or implant location did not manage to explain the heterogeneity. In addition, the variations in osteoporotic models resulted from the time between ovariectomy and experimental procedure where most of the studies inserted the implants after 8–14 weeks for rats and rabbits and 12 months for sheep, and one study inserted the implants only after 5 weeks after osteoporosis induction by OVX surgery in rat model, those time points represent diverse stages of osteoporosis; hence, these comparisons are heterogeneous. Furthermore, only eight studies confirmed the successful establishment of the osteoporotic condition.

The current systematic review included several limitations. Firstly, only one study evaluated implants placed in the jawbones, while the remaining studies used the tibia and/or femur. Secondly, although several studies have reported significant enhancement in bone architecture and implant osseointegration when Sr concentrations were increased from 0% Sr to 100% Sr in the implant surface [36, 37], many studies neglected to mention the Sr concentration in the intervention groups. So, we couldn't conclude the ideal Sr concentration that should be used to enhance the osseointegration. Thirdly, none of the implants in the included studies were loaded. Therefore, future studies should be performed to evaluate the effect of Sr-coated implants under loading conditions, and to identify the ideal coating methods for incorporating Sr into the implant surface, and the ideal Sr concentrations. Furthermore, clinical evaluations based on well-designed randomized controlled clinical trials are required to address the effect of strontium coating of titanium implants in enhancing the osseointegration in patients with osteoporotic conditions.

CONCLUSION

In summary, the present results provide evidence that strontium-coated titanium implants enhanced the osseointegration in animal models under osteoporotic condition as this surface modification techniques have improved the mechanical and biological properties of the titanium implants.

DATA AVAILABILITY

All generated data in this research are available upon request.

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AUTHOR CONTRIBUTIONS

OS did study conceptualization. OS and MA performed study design. MA and AE performed data analysis. YE and HA wrote the main manuscript. All authors reviewed the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The authors declare no conflicts of interest. The manuscript is an electronic-based search and analysis study of the literature. Ethical approval and IRB number were not required.

ADDITIONAL INFORMATION

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