Acta Biomaterialia xxx (xxxx) xxx

Contents lists available at ScienceDirect

Acta Biomaterialia

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

Osseointegration Pharmacology: A Systematic Mapping Using Artificial Intelligence

Mohammed Mahri[a,b], Nicole Shen[a], Francisco Berrizbeitia[c], Rania Rodan[a,d], Ammar Daer[a], Matthew Faigan[a], Doaa Taqi[a], Kevin Yang Wu[a,e], Motahareh Ahmadi[a], Maxime Ducret[a,f], Elham Emami[a], Faleh Tamimi[a,g,*]

[a] Faculty of Dentistry, McGill University, Montreal, QC, Canada
[b] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Jazan University, Jazan, Saudi Arabia
[c] Concordia University, Library, Montreal, QC, Canada
[d] Royal Medical Services, King Hussein Medical Center, Jordan
[e] Faculty of Medicine, Laval University, Quebec City, QC, Canada
[f] Université Claude Bernard Lyon 1, Faculté d'Odontologie, Lyon, France
[g] College of Dental Medicine, Qatar University, Doha, Qatar

ARTICLE INFO

Article history:
Received 14 July 2020
Revised 4 November 2020
Accepted 5 November 2020
Available online xxx

Keywords:
osseointegration
dental implants
pharmacological agents
artificial intelligence
automated screening
machine learning
bone-implant contact
systematic mapping
drugs
prosthetic implants

ABSTRACT

Clinical performance of osseointegrated implants could be compromised by the medications taken by patients. The effect of a specific medication on osseointegration can be easily investigated using traditional systematic reviews. However, assessment of all known medications requires the use of evidence mapping methods. These methods allow assessment of complex questions, but they are very resource intensive when done manually. The objective of this study was to develop a machine learning algorithm to automatically map the literature assessing the effect of medications on osseointegration. Datasets of articles classified manually were used to train a machine-learning algorithm based on Support Vector Machines. The algorithm was then validated and used to screen 599,604 articles identified with an extremely sensitive search strategy. The algorithm included 281 relevant articles that described the effect of 31 different drugs on osseointegration. This approach achieved an accuracy of 95%, and compared to manual screening, it reduced the workload by 93%. The systematic mapping revealed that the treatment outcomes of osseointegrated medical devices could be influenced by drugs affecting homeostasis, inflammation, cell proliferation and bone remodeling. The effect of all known medications on the performance of osseointegrated medical devices can be assessed using evidence mappings executed with highly accurate machine learning algorithms.

Introduction

Osseointegrated devices anchored to bone, such as dental implants, orthopedic prostheses, and cochlear implants, are used to treat several conditions, including tooth and hearing loss, or joint problems. Many patients worldwide are treated with these devices, more than 24,000 total hip replacements surgeries are performed annually in Canada alone (1), and about 100,000-300,000 dental implants and over 96,000 cochlear implant devices are placed in the United States every year (2-4). The success of these devices relies on a phenomenon called osseointegration, which is defined as an intimate contact between the surface of the implant and bone without interposed soft tissues (5). Recent studies have shown that some medications could affect osseointegration and implant survival by interfering with the pathways that regulate bone metabolism and healing (6). This is becoming an issue since a sizable portion of patients treated with osseointegrated devices suffer from conditions that require medication (7). Identifying all drugs known to affect osseointegration in the literature could help make better informed clinical decisions and guide research on osseointegration pharmacology(8). This would help reduce implant failure in patients taking detrimental medications and develop pharmacological interventions to improve osseointegration. Indeed, the effect of medications on the performance of implanted biomaterials is of paramount importance to producers of medical devices. This is particularly relevant considering the recent normative changes of ISO 10993, which requires them to produce a thorough literature analysis prior to any biocompatibility testing. In this context the side effects of medications on medical devices should be identified and reported by suppliers and manufacturers.

* Corresponding author. Tel.: +1 (514) 398-7203 ext.
E-mail address: faleh.tamimimarino@mcgill.ca (F. Tamimi).

https://doi.org/10.1016/j.actbio.2020.11.011
1742-7061/

However, complex open questions such as “what drugs affect osseointegration?” are too extensive for conventional systematic reviews. Evidence mapping reviews were developed to address this type of questions (8). This approach consists of mapping the entire medical literature for abroad medical questions and visualize a thematic area to establish what is known and not known about the effects of an intervention. However, the size of the scientific literature is enormous; thus, full systematic mapping and subject-wide evidence synthesis are usually not feasible (9), and previous efforts have been limited because they require extensive crowdsourcing (9).

Recent advances in artificial intelligence and machine learning could help accelerate the systematic review process by full or semi-automation of the different steps involved in a systematic review (9, 10). Indeed, many different machine learning (ML) algorithms have been developed to automate screening of systematic reviews (11). These algorithms use text mining to estimate the probability of including or excluding an article based on the inclusion and exclusion decisions made by humans (12). However, most of the algorithms require very large training datasets (i.e., up to 5,749 records) (13), and they are only able to reduce the number of abstracts requiring manual screening by about 50% (14), saving only 30% to 70% of the workload (15).

Very recently, ML has also been used for fully or semi-automated evidence mapping reviews. For example, Lama et al. published an evidence mapping review on the effect of low-calorie sweeteners (LCS) on health (16). This mapping review used a semi-automated machine learning approach to tag and categorize the included articles. However, they had to screen 28% of their articles to train their algorithms. Also, the clinical search engine Tripdatabase.com has developed an artificial intelligence (AI) for full automation of evidence mapping (17). However, this prototype has not been validated, and it can only perform automated evidence synthesis for RCT and SR, and it cannot identify and synthesize observational or animal studies (17).

The performance of an AI for text mining depends on the quality of the training datasets and the text used for mining (18). Unfortunately, traditional search strategies used for systematic reviews results in articles that are very similar, which compromises the quality of the training datasets, and the vocabulary used in the scientific literature is often inconsistent and not well controlled.

Based on these observations, we hypothesize that using training datasets with a controlled vocabulary and rich in non-similar documents could help overcome the limitations of machine learning algorithms in systematic reviews and systematic mappings.

Medical Subject Headings (MeSH) is a comprehensive controlled vocabulary for indexing journal articles in health sciences that serves as a thesaurus to facilitate searching. Very recently, PubMed has started to use an Artificial Intelligence based on "natural language understating" to generate high-quality MeSH terms (19). Indeed, ML classifiers using PubMed MeSH terms allow for versatile machine learning approaches to screen the scientific literature with promising results surpassing most of the current methods (20).

The objective of this study was to provide a systematic evidence mapping of the literature to address the question, “What drugs could affect bone-implant osseointegration?”. To achieve this, we developed a method to generate a ML classifier for automated article screening. This classifier used MeSH terms and training datasets with similar and non-similar articles.

Materials and Methods

Study design

This study involved four main steps; manual article screening, ML articles screening, validation of algorithm, and evidence synthesis (see workflow diagram in Appendix B). Our evidence mapping adhered to the PRISMA-Extension for Scoping Reviews (21), and it was carried out according to the methodology of Global Evidence Mapping (GEM) (22), adding suggested components from Ballesteros et al. (23). In this study, we used three different search strategies: two specific search strategies, one designed to retrieve similar documents, and another designed to retrieve non-similar documents, as well as an extremely sensitive search strategy designed to retrieve any relevant documents. The articles retrieved from the specific search strategies were screened manually, whereas the articles identified with the sensitive search strategy were screened using ML. The included studies underwent in-depth syntheses for study design, drug name, type of study, type of implant, drug doses, route of drug administration, study measurements, study outcomes (i.e., the effect of the drugs on osseointegration) and the study quality.

Search strategy (step 1 and 2)

An electronic search of MEDLINE through the PubMed interface was performed on July 1, 2018 and updated on August 31, 2020, using three different search strategies as described in Appendix A:

- Search strategy A: a specific search strategy designed to obtain similar articles. This strategy was focused solely on the MeSH-term “osseointegration/drug effects.”
- Search strategy B: a specific search strategy designed to obtain non-similar articles. This strategy included an independent search of 553 classes of drugs in PubMed ("Pharmacological actions”) and combined them with the MeSH-term "Dental Implants."
- Search strategy C: an extremely sensitive search strategy designed to obtain all articles related to osseointegration. This strategy was designed to identify all relevant articles. However, it retrieved many irrelevant ones that could increase the workload if screened manually.

Eligibility criteria (step 1 and 2)

We included articles assessing the effect of drugs on bone-implant osseointegration in both human and animals. The inclusion criteria were randomized control clinical trials and observational studies on human subjects as well as animal studies assessing the effect of all known drugs on implant survival/success, or bone-implant contact. The exclusion criteria were studies on drugs applied locally, case reports, letters, comments, cross-section studies, editorials, reviews, or conference abstracts, as well as studies on cancer, metastasis, or osteonecrosis.

Screening Method (step 1 and 2)

The articles obtained with the specific search strategies A and B were screened manually by two independent calibrated reviewers (MM, AD) according to our inclusion and exclusion criteria (Figure 1). Disagreements between reviewers were referred to a third reviewer (FT). The articles retrieved with the highly sensitive search strategy were screened automatically using a machine learning algorithm trained with the articles that were screened manually, as described below.

Development of a method for automatization of data screening (step 2)

A script was created in Python to extract from PubMed the metadata of the articles found with the specific search strategies,

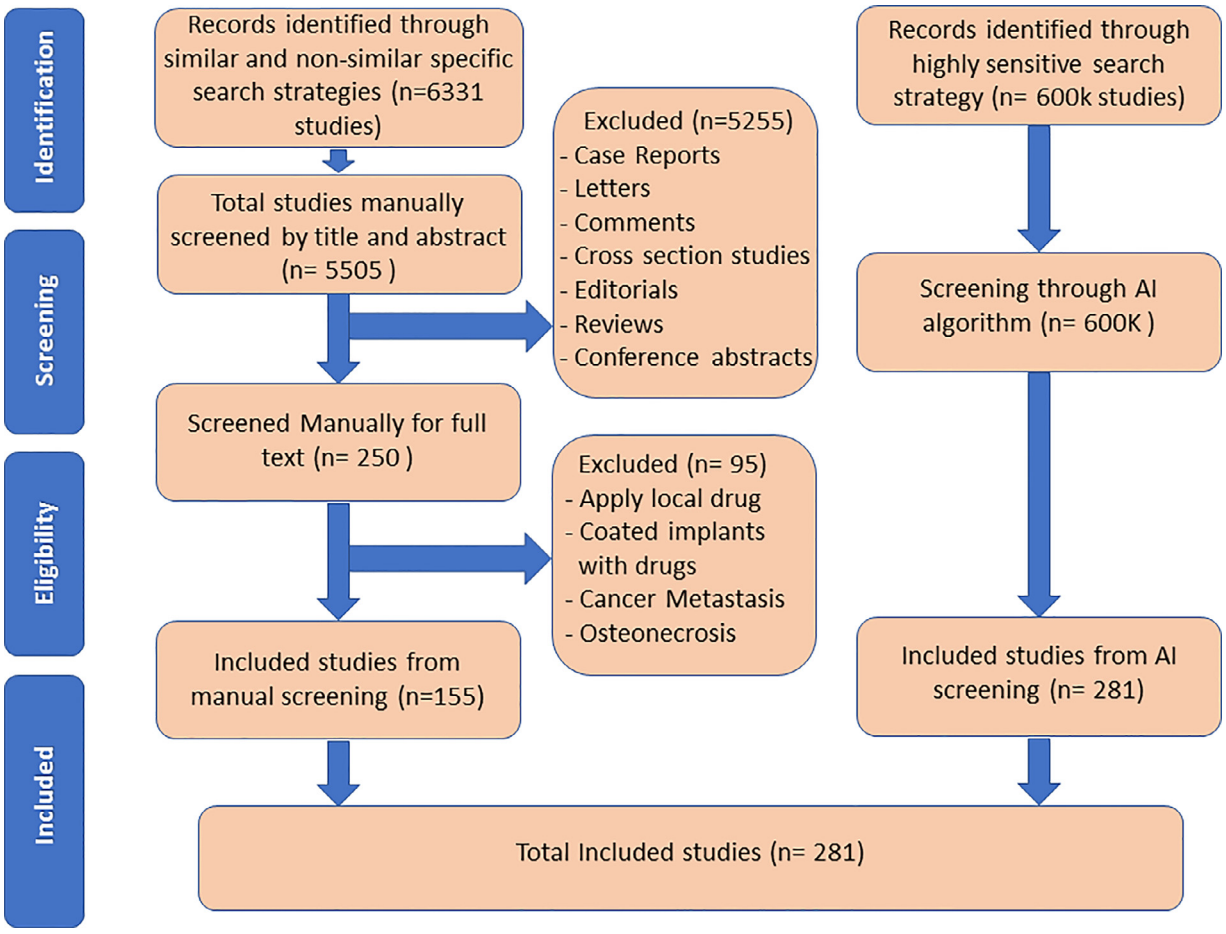

Figure 1. Flow diagram of the study selection process (the graphs show the combined data of both animal and clinical studies).

this included article title, abstract, keywords, and MeSH-terms. The articles were then classified manually into 'included or excluded' and then used to train a machine-learning algorithm using the software Waikato Environment for Knowledge Analysis (WEKA) developed at the University of Waikato, New Zealand (24). Weka is a widely used open-source machine learning platform that allows us to test, build, and compare different machine learning models (25). We used a support vector machine (SVM) algorithm due to its well-established effectiveness in text mining (26). In our preliminary work, we identified that the best results for classification were obtained by training the algorithm using the publication "MeSH terms," probably because the MeSH terms produced by PubMed use a natural language understanding AI that incorporates relevant semantic value (19).

Manual screening resulted in the exclusion of most articles, and only a small portion was included. This skewing of data resulted in imbalanced training datasets (i.e., a high proportion of irrelevant papers) that impaired the ML classifier (27). To address this issue, we selectively penalized false negatives in the selection process, and we balanced the training dataset. Active prioritization and random sampling were also used to improve the performance of the classifiers (28).

The algorithm obtained with the training datasets described above was used for automated screening of the 599,604 articles retrieved with the highly sensitive search strategy (search strategy C). The articles were screened in batches of 100,000 articles (Figure 2). After the automated screening of a given batch, the articles included by the algorithm were screened manually for verification (Figure 2). The results of this manual screening were added to the training datasets, and the algorithm was updated accordingly (Figure 2). The process was repeated with subsequent batches until no more new articles could be identified by the algorithm (Figure 2).

Validation of the method for automated data screening (step 3)

To validate the method developed for automatic screening, we tested the algorithm against an already published systematic review with a search strategy that falls within the scope of ours (29). The included and excluded articles in this previous systematic review were kindly provided by the authors (Appendix C) and used estimate its accuracy, sensitivity, and specificity of our algorithm.

Data Extraction (step 4)

After study selection, the characteristics of each included article were extracted (see Appendix D), and the research questions of each study was extracted using the PICO framework (30). Only articles providing a research question, the elements of the PICO framework and a conclusion of the drug effects on bone-implant osseointegration were included. The conclusions of the included articles were divided into three categories depending on the outcome, similarly to previous studies (23). If the conclusion of the included articles showed clearly and in an indicative language that the drug enhanced or improved the bone-implant osseointegration, we considered the outcome as a "positive effect." If the conclusion of the included article showed clearly and in indicative language

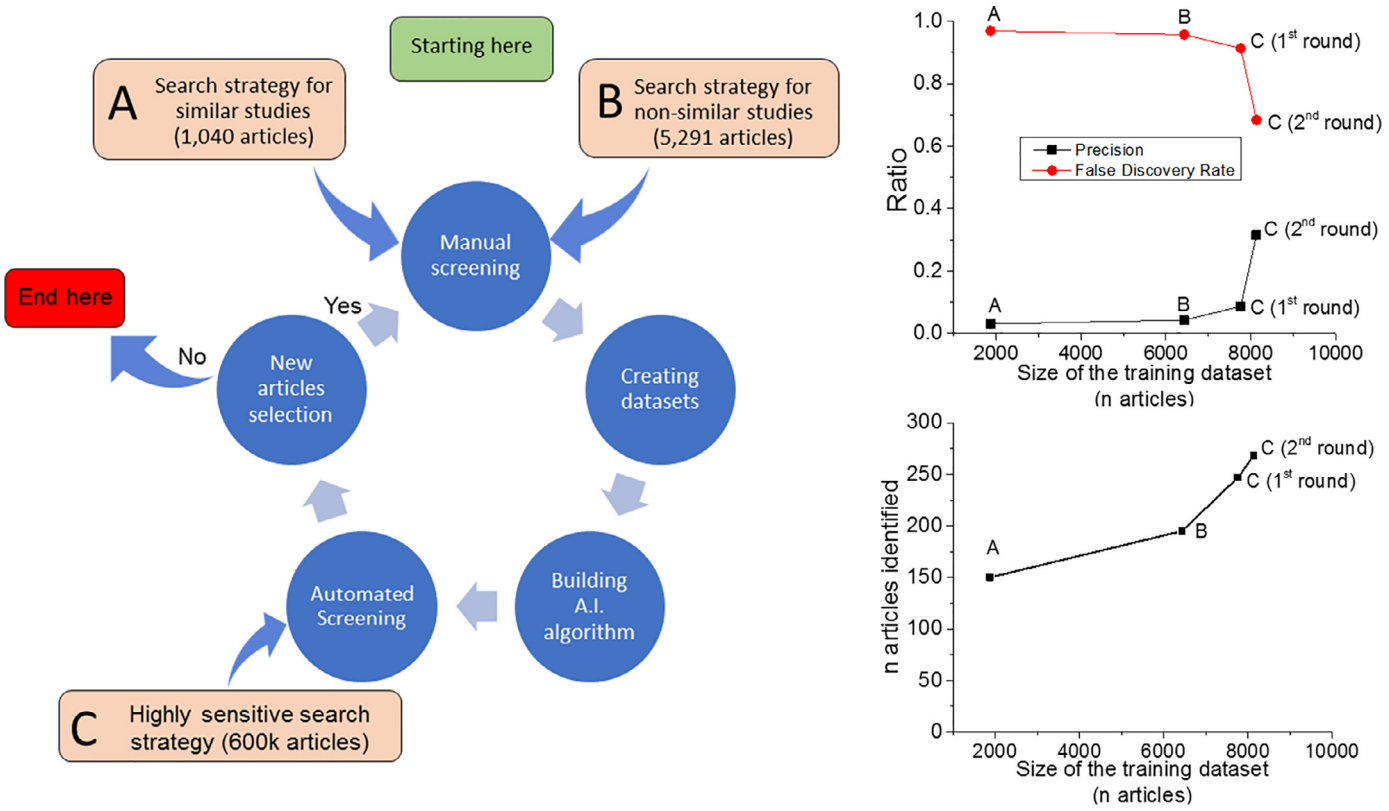

Figure 2. Workflow diagram showing the process of screening the literature in our systematic mapping (left) and performance of the algorithm as a function of the size of the training dataset (right). The training dataset was increase in 4 main steps, first with the articles screened from search strategy "A", then of the articles for Search strategy "B" and followed by the first round of articles screened from search strategy "C" and the second round of articles screened from search strategy "C". Graph depicting the precision (positive predicting value) and the false discovery rate reveals that as the size of the training datasets increased, the precision increased, and the false discovery rate decreased. Also, the number of included articles identified by our algorithm increased reaching a maximum at 281 articles with a training dataset of 8.12k articles, and the false-positive articles were reduced from 6449 to 20 articles. The graphs show the combined data of both animal and clinical studies.

that the drug impaired or negatively influenced bone-implant osseointegration, we considered the outcome as a "negative effect." Finally, If the conclusion of the included articles did not show clearly that the drug either improved or impaired osteointegration, or it showed that the drug had no effect on bone-implant osseointegration, neither negative nor positive, we considered the outcome as "no effect."

Quality assessment and risk of bias (step 4)

Two reviewers assessed the quality of all selected studies independently (AD, RR). Disagreements between the two reviewers were referred and discussed with a third reviewer (FT). The animal studies were assessed according to SYRCLE's guidelines (31), clinical trials were assessed using Cochrane risk of bias tool for randomized controlled trials (32), and the STROBE quality assessment tool was used for observational studies (33).

Evidence mapping presentation (step 4)

The characteristics of the included studies, their main outcomes, and their quality assessments were described on tables and in a narrative description. Bubble plots were used to represent the number of studies per drug, their quality, and their effect on osseointegration. The bubble charts showed the information in three dimensions: 1) the x-axis represented the effect of drugs on bone-implant osseointegration as "negative," "no effect," "positive"; 2) the y-axis represented level of evidence per each drug as "poor," "fair," "good"; and 3) the number of studies included for each drug was represented by the bubble size.

Results

Study Selection

The search strategy A identified 1040 articles, the search strategy B identified 5291 articles, and the search strategy C identified 599,604 articles. The 6331 articles identified with the search strategies A and B were screened manually, 250 articles were selected for full-text assessment, and 155 were included. The datasets of included and excluded articles were then used to train a machine-learning algorithm to screen the articles identified with the search strategy C (599,604 articles) (Figure 1). The initial performance of the algorithm presented a low precision; however, after each reiteration, we increased the size of the training dataset, and the algorithm recall and precision improved progressively until reaching a plateau beyond which the algorithm was not able to identify new articles. This was achieved by screening 8121 articles, 1.49% of the total dataset. Eventually, a total of 281 studies were finally selected; this included the 155 articles retrieved by manual screening of the articles retrieved with the specific search strategies and another 126 articles that were only identified using our AI algorithm (Figures 3). Among the included studies, there were 204 animal studies and 77 human studies. The included studies assessed 31 drugs, 29 drugs were investigated in animals, and 14 in humans. Eight of these drugs were also used in combination with other drugs (Table 8 is available in Appendix H).

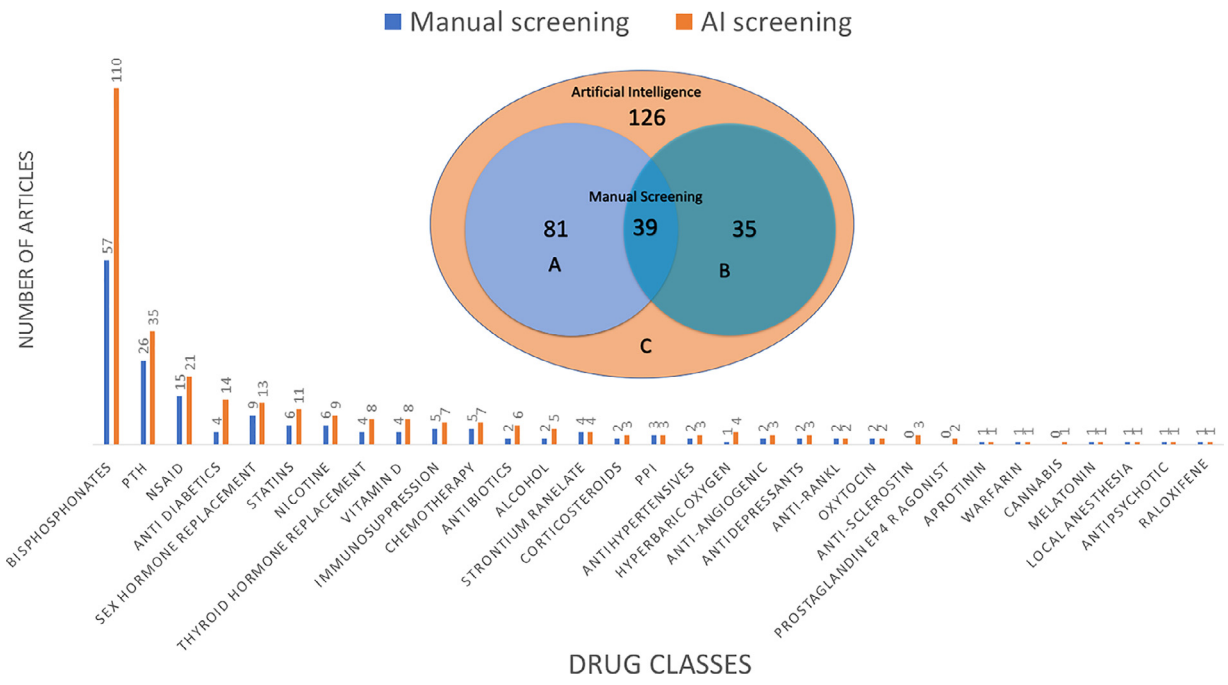

Figure 3. Venn diagram showing the number of articles identified with each screening method and search strategy. A- represents the articles screened manually from the specific search strategy for similar studies, B- represents the articles screened manually from the specific search strategy for non-similar studies, C- represents the new articles screened by AI from the highly sensitive search strategy. Besides, the graph depicting the number of studies included for each drug as a function of the screening methods (A.I. or manual screen). The graphs show the combined data of both animal and clinical studies.

Validation of the method for data screening

The algorithm was able to identify 13 of the 17 articles included in the previously published systematic review, and it discarded 3of the 17 articles included because they fit our exclusion criteria (i.e. case reports, studies on osteonecrosis, analysis of risk factors for cluster behavior). Only one article was incorrectly discarded by the algorithm as a false negative. The algorithm revealed an accuracy of 95%, a False Positive Rate (TFP) of 95%, a precision of 30%, a sensitivity of 93%, and a specificity of 95%, and it reduced the workload by 95% (Appendix C).

Quality of the evidence

The quality assessment of the studies was stratified according to drug category and type of study. RCTs on NSAID, Bupivacaine, Bisphosphonates, Parathyroid hormone replacement therapy, Vitamin D, and Thyroid hormone replacement therapy presented poor-to-fair quality, and the RCT on Antibiotics (amoxicillin) was the only one that showed good quality (Figure 4, Appendix E). Observational studies on Bisphosphonate, NSAID, Chemotherapy, Vitamin D, Antibiotics (Penicillin), Xianlinggubao, as well as Thyroid and Parathyroid hormone replacement therapies presented high-to-moderate risk of bias. Observational studies on Antihypertensives, SSRI, Statins, and PPI presented low-to-moderate risk of bias, and those on Corticosteroid, Testosterone, and Estrogen hormone replacement therapies presented moderate risk of bias (Figure 4, Appendix F). Animal studies assessing Bisphosphonate, NSAID, Chemotherapy, Immunosuppressants, Statins, Aprotinin, as well as Sexual, Thyroid and Parathyroid hormone replacement therapies, Nicotine, Strontium ranelate, Vitamin D, Sclerostin antibody, Oxytocin, Warfarin, Anti Diabetic, Alcohol, Antihypertensives, Antibiotics, Hyperbaric oxygen therapy (HBO), Prostaglandin EP4 receptor agonist, Cannabis, Melatonin, Lithium chloride, and Corticosteroid presented high-to-moderate risk of bias (Figure 4 and Appendix G). Animal studies on Proton-Pump Inhibitor (PPI), Aprotinin, and Anti-vascular endothelial growth factors (VEGF) presented low to moderate risk of bias (Figure 4, Appendix G). The qualitative synthesis summary of the collected data is shown in three analyses: RCT studies, observational studies, and animal studies.

Synthesis of results: Drugs effects on bone-implant osseointegration

Underneath were described in detail the findings on each of the drugs identified in our review.

Anti-osteoporosis Drugs

Bisphosphonates: Unspecified bisphosphonates were associated with low risk of implant failure in four cohort studies, three retrospective ones on arthroplasty, and a prospective one on lumbar fusion (34-37). However, they were also associated with high risk of implant failure in a cohort studies on dental implants (38, 297), and had no significant effect on implant failure in six retrospective cohort studies on dental implants (39-44). The literature on the specific types of bisphosphonates assessed for their impact on osseointegration is discussed below.

Zoledronic Acid: Zoledronic acid (4 and 5 mg) was associated with low risk of implant failure in three Randomized Control Trials (two double-blinded and one open-label), two on total hip arthroplasty and one on dental implants (45-47). However, a dose of 5 mg had no significant effect on implant failure in one prospective study on dental implants (48).

In thirteen animal studies, pre-operative, and post-operative intravenous and subcutaneous administration of zoledronic acid (0.01-0.6 mg/kg/every 3-4 weeks) had enhanced osseointegration by increasing bone-to-implant contact, peri-implant bone volume, removal torque force (49-61). Five of these studies were on rats (four of them on ovariectomized rats), six studies on rabbits (three

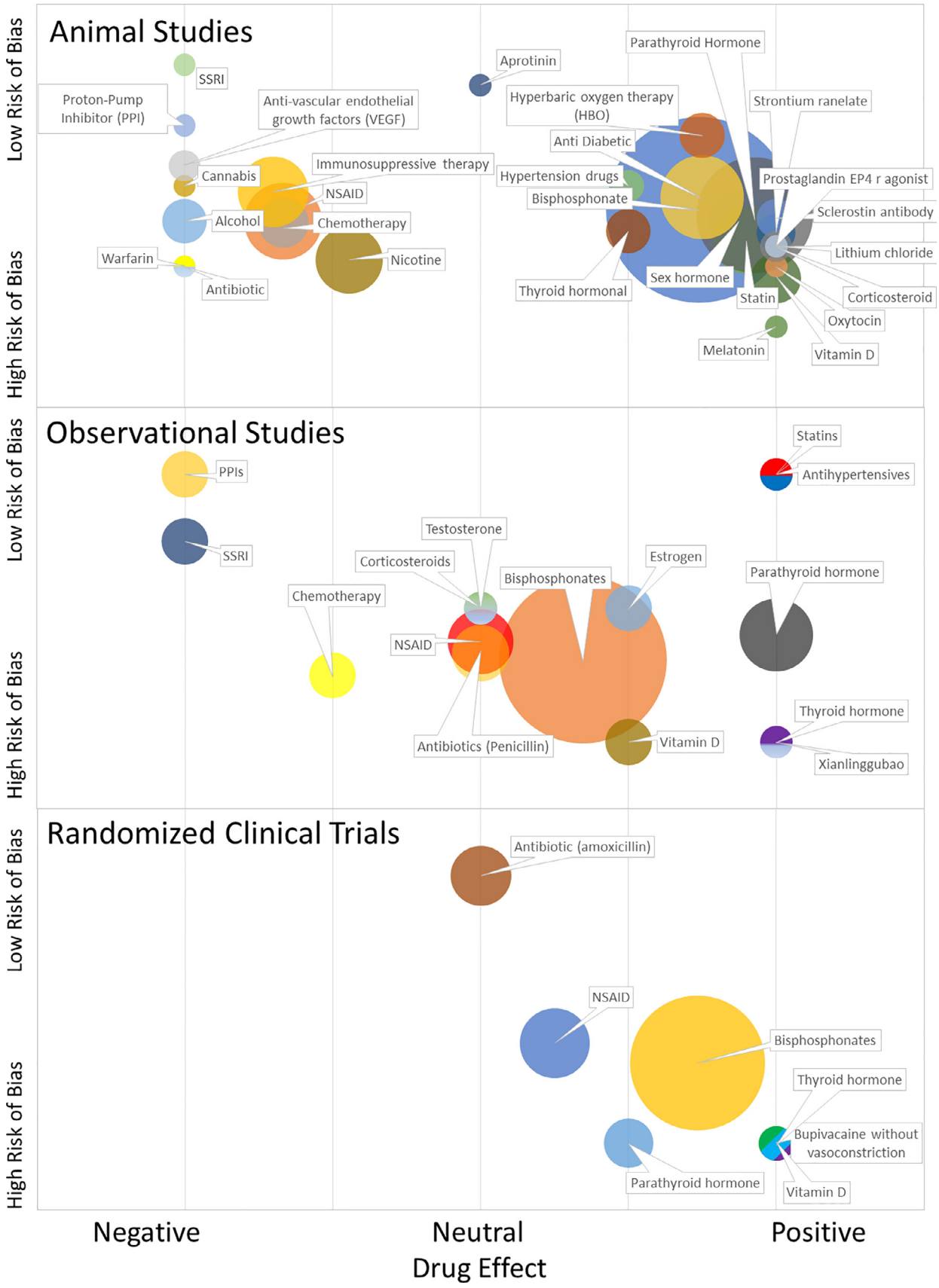

Figure 4. Bubble plot for RCT, observational studies, and animal studies representing the number of studies per drug, the quality of the studies, and the effect of the drugs on osseointegration for each study. The y-axis represents the quality of the study according to the risk of bias tool. The x-axis notates the drug effect on osseointegration. The size of the bubble indicates the number of articles per drug. When the bubble shows more than one color it means there are two or more different drugs that have the same number of studies, the same quality, and the same effect on osseointegration.

of them on ovariectomized rabbits), one on dogs, one on sheep, and one on mice. Five of these studies used Hydroxyapatite (HA)-coated titanium implants, four used screw titanium implants, three used nonspecific titanium implants, one used titanium rods, and one used cylindrical porous implant. On the other hand, pre-operative, and post-operative administration of zoledronic acid (0.0066-0.1 mg/kg/every 0.5-4 weeks, IV and IP) was found to have a negative effect on osseointegration in five animal studies assessing bone-to-implant contact and peri-implant bone volume (62-65, 301). Two of these studies were on dogs, one on rabbits, one on rats, and one on sheep. Four of these studies used screw titanium implants, and one used Hydroxyapatite (HA)-coated titanium implants. Postoperative intravenous and subcutaneous administration of zoledronic acid (0.0075-0.1 mg/kg/every week) was found to have no effect on osseointegration in two animal studies (66, 67), one on ovariectomized rats and the other one on non-ovariectomized rats. One of these studies used dental titanium implants, and the other one used cylindrical titanium implants. Bone-to-implant contact, peri-implant bone volume analyses showed that zoledronic acid had no effect on BIO. Preoperative intramuscular administration of zoledronic acid (0.01 mg/kg/twice a week) combined with dexamethasone (1 mg/kg/ twice a week) was found to impair osseointegration in one study on rabbits (65). However, postoperative administration of zoledronic acid (7.5 μg/kg/once a week, IV) combined with dexamethasone (1 mg/kg, IM) was found to have no effect on osseointegration in one study on rats (67). Moreover, postoperative administration of zoledronic acid (7.5 μg/kg/once a week, IV) combined with methylprednisolone (0.35 mg/kg, SC) was found to enhance osseointegration in one study on rabbits (68).

Alendronate; In human studies**,** alendronate (5-35 mg/day, or 70 mg/ week) was associated with low risk of implant failure in a retrospective study on total knee arthroplasty, two prospective studies on total hip arthroplasty and total knee arthroplasty, respectively, and eleven Randomized Control Trials, nine on total hip arthroplasty, and two on total knee arthroplasty (69-82). Also, the combination of alendronate (70 mg/once a week) and Xianling gubao (phytoestrogen-rich natural product) (three times a day) was associated with low risk of implant failure in a Randomized Control Trial on total hip arthroplasty (83). However, the use of alendronate (4, 6, or 10 mg/day) was associated with high risk of implant failure in two retrospective cohort studies on dental implants (84, 85), and its use (10 mg/a day, or 70mg/week) had no significant effect on implant failure in two Randomized Control trial studies on total knee arthroplasty and two retrospective cohort studies on dental implants (86-89).

In animal studies, pre- and post-operative oral, intraperitoneal and subcutaneous administration of alendronate (0.02-10 mg/kg/daily, 0.2-10 mg/kg/once a week, 0.07-1 mg/kg/twice a week, and 0.0025-5mg/kg/three time a week) was found to enhance osseointegration in twenty-seven animal studies (49, 90-114, 293, 303). Twenty-two studies on rats (thirteen of them on ovariectomized rats), three on dogs, two studies on rabbits (one of them on ovariectomized rabbits and one on non-ovariectomized rabbits), and one on pigs. Eighteen of these studies used titanium implants (9 screws, 3 Hydroxyapatite (HA)-coated, 5 cylindrical, one costume), two used screw non-titanium implants, one used titanium plates, one used polyethylene implants, one used cylindrical polymethylmethacrylate plugs, one spine pedicle screws, one used stainless-steel implants, one used Polymethylmethacrylate cement rods implants, and two did not mention the type of implants. Bone-implant contact, peri-implant bone volume, removal torque force test, pull-out force test, and push-out force test analyses showed that alendronate improved BIO. On the other hand, postoperative administration of alendronate (1 mg/kg/twice a week, SC) was found to impair osseointegration of custom-made titanium implants in two animal studies on rats (115, 292).

Moreover, pre-operative and post-operative oral and subcutaneous administration of alendronate (0.063 mg/kg/ daily, 0.1 mg/kg/twice a week, 2.5 μg/kg/ three-time week, 6 mg/kg/daily or 10 mg/kg/once a week) was found to have no effect on osseointegration in five animal studies (116-121). Two of these studies were on rabbits (one of them on ovariectomized rabbits), two on non-ovariectomized rats, and two on dogs (one of them on ovariectomized dogs). Four of these studies used screw-shaped titanium implants, one used titanium plates, and one used cylindrical titanium implants. Bone-to-implant contact and peri-implant bone volume analyses showed that systemic administration of alendronate did not affect BIO.

Disodium Diphosphonate: Postoperative subcutaneous administration of disodium diphosphonate (0.1-5 mg/kg/day) was found to enhance osseointegration of porous titanium fiber-mesh implants in a study assessing bone-to-implant contact and peri-implant bone volume in rabbits (122).

Ibandronate: In animal studies, postoperative administration of ibandronate (1.0-25 μg/kg/day or 700 μg/kg/single dose, SC) was found to enhance osseointegration in five studies assessing bone-to-implant contact and peri-implant bone volume in rats (one of them ovariectomized rats) (123-127). Some of these studies used hydroxyapatite (HA)-coated titanium implants.

Clodronate: Use of clodronate (100, 400, and 1600 mg/kg/daily) was associated with low risk of implant failure in three Randomized Control Trials (two of them double-blinded), two on total knee arthroplasty and one on total hip arthroplasty (128-130). Postoperative subcutaneous administration of clodronate (0.12, and 21 mg/kg/3 times a week) was also found to enhance osseointegration of titanium plates in a study assessing bone-implant contact in rats (96).

Risedronate: In human studies, use of risedronate (2.5 or 35 mg/kg/daily or 35 mg/kg/once a week) was associated with low risk of implant failure in two prospective cohort studies, one on total hip arthroplasty and another on posterior lumbar bone, as well as in two Randomized Control Trials (one of them double-blinded) on total hip arthroplasty (72, 131-133).

On the other hand, use of risedronate (35 mg/kg/once a week) was not associated with implant failure in one double-blind Randomized Control Trial on total hip arthroplasty (134). Moreover, in animal studies, pre-operative and postoperative subcutaneous administration of risedronate (0.1 mg/kg/once every two days) was found to enhance osseointegration of screw titanium implant in a study assessing bone- implant contact and push-out force in ovariectomized rats (97).

Pamidronate: In a double-blind Randomized Control Trial on total hip arthroplasty, use of pamidronate (90 mg/kg) was associated with low risk of implant failure (135). Moreover, postoperative (SC, IM, IV or IP) of pamidronate (0.4, 4, 40, and 500 μg/kg/daily, and 0.6 - 1 mg/kg/once, three or five times a week) was found to enhance osseointegration in five animal studies (four on rats, and two on dogs) assessing bone-to-implant contact, peri-implant bone volume, pull-out force, and push-out force (136-140, 293). Three of these studies used screw titanium implants, one used endotoxin-coated polyethylene particles titanium implants, one did not mention the type of implants, and one used stainless-steel screw-shaped implants.

TRK-530: Postoperative administration of TRK-530 (1 mg/kg/every other day, SC) was found to enhance osseointegration Kirshner (K)-wires in a study assessing bone-implant contact and peri-implant osteolysis in rats (141).

YM-175: Pre- and post-operative administration of YM-175 (10 μg/kg/three times a week, SC) was found to enhance osseointegration of screw-form titanium implants in a study assessing bone-

implant contact and peri-implant osteolysis in ovariectomized rats (142).

Etidronate: In In a double-blind Randomized Control Trial, etidronate (400 mg/kg/day) was not found to be a contributing factor on implant survival in total hip arthroplasty (143).

Parathyroid Hormone Replacement Therapy (PTH): Various doses of PTH replacement therapy (20 μg/kg/daily or 56.5 μg/kg/week, SC) were assessed for their impact on osseointegration. In human studies, use of PTH replacement therapy had no significant effect on dental implant failure in a single-blinded open-label randomized controlled feasibility study (144). However, PTH had a positive effect in a retrospective study on total knee arthroplasty, a Randomized Controlled Trial on total hip arthroplasty, three cohort studies on lumbar interbody fusion pedicle screws and one on total knee arthroplasty (37, 133, 145-147). Also, the use of PTH had a negative effect in a prospective cohort study on dental implant (297).

In animal studies, pre- and post-operative administration of PTH (2-60 μg/kg/daily, 5-60 μg/kg/three time a week, 10-75 μg/kg/five time a week, or 60 μg/kg/six time a week, SC) was found to enhance osseointegration in twenty-six animal studies (60, 110, 137-139, 148-167, 295, 305). Fifteen of these studies were on rats (seven of them on ovariectomized rats), three on low protein diet rats, five on rabbits (two of them on ovariectomized rabbits and one on post-orchiectomy rabbits), three on dogs, and one on mice. Twenty-four of these studies used titanium implants (13 screws implants, 5 (HA)-coated implants, three unspecified implant designs, three cylindrical implants, one roughened surface implant), two used screw-shaped stainless-steel implants, one used cylindrical custom loading device, one used polymethylmethacrylate implants and one used cylindrical cemented titanium plates. Bone-to-implant contact, peri-implant bone volume, removal torque force test, pull-out force test and push-out force test analyses showed that systemic administration of PTH improved BIO.

On the other hand, post-operative administration of PTH (2, 40 and 60 μg/kg/three times a week, SC) had no significant effect on osseointegration in three rat studies (two of them on diabetic rats). These studies used screw titanium implants and they showed that PTH had no significant effect on bone-to-implant contact (168-170). Moreover, two studies on rats (one on ovariectomized rats) showed that combined administration of simvastatin (5 and 25 mg/kg daily) with PTH (60 and 40 μg/kg, 3 times/ week) enhanced osseointegration (161, 162) . Also, in another study, PTH (40 μg/kg/day/three days a week, SC) enhanced osseointegration in rats smoking nicotine. (164).

Vitamin D: In two single-blinded Randomized Control Trials on total hip arthroplasty, vitamin D use (1 mg/day) was not associated with increased survival of osseointegrated implants (74, 82).

In animal studies, pre-operative and post-operative administration of vitamin D (calcitriol) (0.1-60 μg/kg, IP, oral and SC) enhanced osseointegration in five animal studies assessing bone-to-implant contact, bone mass, pull-out force test, and push-out force analyses on titanium implants (two screw-shaped, one unspecified design, one hydroxyapatite-coated, and one rod-shaped implants) (104, 171-174). Three of these studies were on ovariectomized rats, one on diabetic mice, and one on diabetic rats. Also, combining this drug with insulin (3.5 IU/twice a day, SC) resulted in improved BIO in one study on diabetic rats (171), and combining it with bisphosphonates (3.5 IU/twice a day, SC) improved BIO in a study on ovariectomized rats (104).

On the other hand, one study on rats showed that vitamin D deficiency has a negative impact on the osseointegration of cylindrical hydroxyapatite-coated titanium implants (175).

Anti-Sclerostin antibody: Post-operative administration of sclerostin antibody therapy (25-100 mg/kg/ once or twice a week, SC) was found to enhance osseointegration in three studies assessing Bone -implant contact, peri-implant bone volume, removal torque force test, and pull-out force test analyses in rats (176, 177, 298). One of these studies used rod-shaped titanium implants, one used screw titanium implants, and one used cylindrical titanium implants.

Anti-RANKL: Post-operative administration of anti-RANKL (OPG-Fc) (8-10 mg/kg/twice a week, SC) was found to enhance osseointegration in two studies on rats (103, 178). One of these studies used stainless-steel screw implants, and the other one used cylindrical titanium plate plugs, and they assessed bone-implant contact, peri-implant bone density, and the pull-out test force.

Strontium ranelate: In animal studies, post-operative systemic administration of strontium ranelate had a positive effect on bone-implant osseointegration in four studies on rats (one of them on ovariectomized rats). These studies used daily oral doses of 500-1000 mg/kg/day for 8-12 weeks after implant placement. Two of these studies used hydroxyapatite-coated titanium implants, and the other two studies used titanium screw or rod-shaped implants. Bone-to-implant contact, bone volume surrounding the implants and pull-out test analysis showed that strontium ranelate improved BIO (49, 179-181).

Analgesics

NSAID: Unspecified NSAIDs have been shown to have negative effects on the marginal bone around dental implants in one retrospective cohort study (182). However, on another retrospective cohort study, NSAIDs significantly increased the crestal bone levels around hydroxyapatite-coated implants (183). Underneath, we discuss the literature on specific types of NSAIDs.

Meloxicam: In animal studies, post-operative subcutaneous and intramuscular administration of meloxicam (3mg/kg/day) had a negative effect on bone-implant osseointegration in two studies on rats (184, 185). These studies used screw-form titanium implants and showed that meloxicam impaired bone-to-implant contact and bone area within the implant threads.

On the other hand, post-operative intramuscular administration of meloxicam (0.2mg/kg) did not show significant effects on bone-implant osseointegration in one study on rats (186). This study used screw-form titanium implants, and it showed that meloxicam had no significant effect on the bone area within the threads of the implants.

Diclofenac sodium: In animal studies, post-operative administration of diclofenac sodium (1.07 mg/kg twice a day or 30mg/kg/day, IM) impaired osseointegration in two studies on rats and in another one on rabbits (186, 187). One of these studies used cylindrical HA-coated titanium implants, and the other used screw-shaped titanium implants. The bone-to-implant contact, the bone area within the implant threads, and the pull-out test analyses showed that diclofenac sodium impaired bone-implant osseointegrations. On the other hand, post-operative oral and intramuscular administration of diclofenac sodium (2 and 5 mg/kg/day) did not show a significant effect on osseointegration in two other studies on rabbits (188, 189). These studies used cylindrical titanium implants, and cylindrical HA-coated titanium implants, and they assessed bone-to-implant contact, bone volume and pull-out test analyses.

Aspirin: Post-operative administration of aspirin (17 or 34 mg/kg/day for 2, 4, and 8 weeks, SC) impaired osseointegration of porous-coated chrome-cobalt implants in a study assessing bone-implant contact and bone ingrowth in rabbits (190).

Ibuprofen: Use of ibuprofen (400 mg/kg, 3 times/day or 600 mg/kg, 4 times/day) was not associated with a higher risk of implant failure in one prospective cohort study on dental implants

and two double-blind Randomized Control trials, one of them on total hip arthroplasty and the other one on dental implants (191-193).

Post-operative administration of ibuprofen (17 or 34 mg/kg/day for 2, 4, and 8 weeks, SC) impaired osseointegration of porous-coated chrome-cobalt implants in a study assessing bone- implant contact and bone ingrowth in rabbits (190).

Celecoxib: Use of celecoxib (200 mg/ twice a day) was not associated with higher risk of implant failure in two double-blind Randomized Controlled trials on total hip and knee arthroplasty respectively (194, 195). Postoperative oral administration of celecoxib (3 mg/kg/day) did not show any effect on osseointegration of cylindrical HA-coated titanium implants in rabbits' femora (189). Also, postoperative oral administration of celecoxib (10 or 25 mg/kg/day) reduced implant debris-induced inflammation and osteolysis around titanium implants in mice (196).

Indomethacin: Pre- and post-operative administration of indomethacin (1-10 mg/kg/day, SC) impaired osseointegration in three animal studies, two on rabbits and one on ovariectomized rats (97, 190, 197). These studies used porous-coated chrome-cobalt implants, cylindrical titanium implants, and screw implants, respectively, and the analyzed bone-implant contact, bone ingrowth, and push-out force. On the other hand, pre-operative, and post-operative administration of indomethacin (1 and 4 mg/kg/day, SC, Oral) did not show any effect on osseointegration in a study on rabbits and another one on dogs (198, 199). These studies used cylindrical titanium implants, and they assessed bone-implant contact and peri-implant bone density.

Naproxen: Post-operative oral administration of naproxen (110 mg/kg/day) did not affect osseointegration of cylindrical titanium chambers in a study in rabbits (200).

Rofecoxib-A: Post-operative oral administration of rofecoxib-A (12.5 mg/kg/day) had no effect on osseointegration of cylindrical titanium chambers in rabbits (200).

Parecoxib: Post-operative use of parecoxib (1.5 mg/kg/day, SC) had no effect on osseointegration of cylindrical titanium implants in a study assessing bone-implant contact in rabbits (188).

Flurbiprofen: In a double-blind Randomized Controlled Trial, flurbiprofen (100 mg/twice a day for a year, oral) after dental implant loading was associated with lower risk of failure (201).

Prostaglandin EP4 receptor agonist: In animal studies, post-operative administration of prostaglandin EP4 receptor agonist (ONO-4819) (15-30 μg/kg/twice a day, SC) enhanced osseointegration in two studies on ovariectomized rats (202)(290). One of these studies used screw-shape hydroxyapatite/titanium composite and titanium-coated rough-surfaced implants and the other study used cylindrical hydroxyapatite-coated implants. Bone-to-implant contact, and pull-out force test analyses showed that prostaglandin EP4 receptor agonist (ONO-4819) improved BIO, especially with rough-surface hydroxyapatite-coated titanium implants.

Cannabinoids*:* Post-operative intermittent inhalation of marijuana (3 g of dried marijuana leaves) was found to impair osseointegration of screw-shaped titanium implants in a study assessing bone-implant contact and bone growth within the implant threads in rats (203).

Local anesthesia (Bupivacaine): In a Randomized Control Trial, use of bupivacaine without vasoconstrictor was associated with an increased survival rate of osseointegrated implants (204).

Psycholeptic Drugs

Melatonin: Post-operative oral administration of melatonin (5 mg/kg/once a day for 8.5 weeks) enhanced osseointegration of screw-form titanium implants in a study assessing bone-to-implant contact and peri-implant bone volume in pinealectomized rats (205).

Lithium chloride: Postoperative Systemic administration of lithium chloride (150 mg/kg/twice a day for 3 months) enhanced osseointegration of cylindrical titanium implants in a study assessing bone-implant contact, peri-implant bone volume, and push-out force in ovariectomized rats (206).

Antidepressant Drugs

Selective Serotonin reuptake Inhibitors (SSRIs): Systemic administration of Selective Serotonin Reuptake Inhibitors (SSRIs) was associated with a higher risk of implant failure in two retrospective cohort studies, and one of them showed significant results (207, 208).

In animal studies, postoperative systemic administration of SSRIs (5 mg/kg/ a day for two weeks) impaired osseointegration of rod-shaped titanium implants in a study assessing bone-to-implant contact and peri-implant bone volume in rats (304).

Drugs Used in Addictive Disorders

Nicotine: In four animal studies, nicotine (1.25 -9 mg/kg, SC) impaired osseointegration, while in four other studies nicotine doses of 0.37 – 0.93, 9, 15 or 85.2 mg/kg did not show any effect. The only study assessing the effect of smoking nicotine found that it had a negative effect on osseointegration. Also, in another study, smoking nicotine combined with PTH (40 μg/kg/day 3 days/week, Sc), showed a positive effect on osseointegration in rats. Moreover, in another study on rats, combined administration of nicotine with daily 10% Gay Loussac ethanol showed a negative effect on bone-to-implant osseointegration (164, 209-217).

Alcohol: Oral administration of ethanol (10% -20%) for 3-4 weeks before implant surgery and 2-9 weeks after implant placement was found to impair osseointegration in five studies assessing bone-implant contact in rats (214, 218-221). Three of these studies used hydroxyapatite-coated implants, and the other two used titanium screw or cylindrical titanium implants. Moreover, in another study on rats combined daily administration of nicotine with 10% Gay-Lussac ethanol showed a negative effect on osseointegration (214).

Sex Hormone Replacement

In a retrospective cohort study, use of unspecified sex hormone replacement therapy was not associated with an increased survival rate of osseointegrated implants (222). Underneath we discuss the literature on the specific types of sex hormone replacement drugs.

Estradiol: In human studies, the use of estrogen replacement therapy was associated with an increased survival rate of osseointegrated implants in one retrospective cohort study, and this association was statistically significant (223). Also, the use of alendronate (70 mg/kg/once a week) combined with Xianling gubao (phytoestrogen-rich natural product) (three times a day) was associated with an increased survival rate of osseointegrated implants in one Randomized Control Trial on total hip arthroplasty (83). Pre-operative and post-operative administration of 17β estradiol (0.02-1 mg/kg/daily or 3 to 4 days a week, SC) was found to enhance osseointegration in nine studies on rats (eight of them on ovariectomized rats) (107, 109, 224-229, 303) . Five of these studies used screw-form titanium implants, one study used titanium nail implant, two studies used titanium micro-implants, and one study used hydroxyapatite-coated screw titanium implants. Bone-to-implant contact, the bone area within the limits of implant threads, peri-implant bone density, removal torque test, pull-out force test and push-out force test analyses showed that 17β estradiol improved bone-implant osseointegration. However, pre-operative and post-operative subcutaneous administration of 17β

estradiol (20 μg/kg/daily) was found to have no effect on osseointegration in one study on ovariectomized dogs and one study on ovariectomized rats (142, 230). One of these studies used cobalt-chromium porous plugs and the other used screw-form titanium implants and they showed that short-term, high-dose estrogen replacement hormone did not affect significantly bone-implant contact and peri-implant bone ingrowth.

Dihydrotestosterone Pre-operative administration of dihydrotestosterone was found to enhance osseointegration of cobalt-chromium-molybdenum implants in a study assessing bone-implant contact and pull-out analyses in rats (231).

Raloxifene: Post-operative oral administration of raloxifene (1.0 mg/kg/day) was found to enhance osseointegration of screw-shaped titanium implants in a study assessing bone-to-implant contact, torque, and bone area within the threads in ovariectomized rats (105).

Thyroid Hormone Replacement

Calcitonin: Calcitonin was associated with increased survival rate of osseointegrated implants in two different clinical studies (232, 233). a prospective cohort study that showed statistical significance and a Randomized Control Trial that showed non-significant results. Regarding animal studies, four studies on ovariectomized rats, assessed the effect of different doses of calcitonin on osseointegration (97, 106, 224, 225). These studies found that different doses of calcitonin (2 -16 IU/kg/day or every 2 days, SC) enhanced osseointegration. Three of these studies used screw-form titanium implants, and the other one used cylindrical HA implants, and they showed that calcitonin improved bone-to-implant contact and the bone area within the threads of the implants. On the other hand, calcitonin (2 IU/kg, daily, IM) impaired osseointegration of screw-shaped titanium implants in a study assessing the initial phase of bone healing around implants in rabbits (234).

Levothyroxine: Pre-operative oral administration of levothyroxine (0.4 IU and 0.18 IU) was found to enhance osseointegration of screw-form titanium implants in a study assessing bone-implant contact in rats (235).

Oxytocin

Post-operative administration of oxytocin (1 mg/kg/day, SC) enhanced osseointegration of machined and grit-blasted rod titanium implants in studies assessing bone-implant contact, peri-implant bone volume, and push-out force in ovariectomized rats (236, 237).

Corticosteroids

Methylprednisolone: Pre- and post-operative administration of methylprednisolone (0.35 mg/kg/three times a week, SC) impaired osseointegration of screw-type titanium implants in a study assessing bone-implant contact and the total peri-implant bone in rabbits (68). However, combining this drug with zoledronic acid (7.5 μg/kg/once a week, IV) enhanced BIO (68).

Prednisolone Pre-operative and post-operative administration of prednisolone (10 mg/kg/daily, IM) impaired osseointegration of screw-type titanium implants in the mandible but did not show any significant effect on osseointegration in the tibia in a study assessing bone-implant contact, bone density, and removal torque in rabbits (238).

Glucocorticosteroids: Different doses of Glucocorticosteroids (5-60 mg) were not associated with higher risk of implant failure in a retrospective cohort study on dental implants (239).

Chemotherapy

Chemotherapy was associated with higher risk of implant failure in a prospective cohort study on 24 non-users and 30 users of chemotherapy receiving combinations of methotrexate, cyclophosphamide, doxorubicin, ifosfamide, cisplatin, etoposide, and various other agents (240) However, no significant effect was observed in another prospective cohort study done on 60 non-users and 30 users of chemotherapy receiving cis- or carboplatin and 5-fluorouracil in three cycles (241). Underneath we discuss the literature on specific types of chemotherapy drugs.

Cisplatin: Pre-operative and post-operative systemic administration of cisplatin (1-150 mg/m^2/once a week) impaired osseointegration in two studies on dogs, one study on rats, and one study on rabbits (242-244, 300). Two of these studies used porous-surface titanium implants and the other two used screw-type titanium dental implants. Bone-to-implant contact, bone ingrowth analyses, and torque force tests showed that cisplatin impaired bone-implant osseointegration.

Methotrexate: Pre-operative intramuscular administration of low dose methotrexate (3 mg/kg/once a week) had no significant effect on osseointegration of screw-shaped titanium implants in a study assessing bone-implant contact and peri-implant bone area in rabbits (245).

Doxorubicin: Pre- and postoperative systemic administration of doxorubicin (20 mg/m^2/once a week) impaired osseointegration of porous-surface titanium implants in a study assessing Bone-implant contact, bone ingrowth, and torque force in dogs (244).

Ifosfamide: Pre- and post-operative systemic administration of ifosfamide (300 mg/m^2/week) impaired osseointegration of porous-surface titanium implants in a study assessing Bone-implant contact, bone ingrowth, and torque force in dogs (244).

Anti-Angiogenic drugs

Different anti-angiogenic medications such as TNP-470, anti-VEGF, and ranibizumab have been assessed for their impact on bone-implant osseointegration.

TNP-470: Post-operative administration of TNP-470 (10 mg/kg/three days a week, SC) impaired BIO of screw-shaped titanium implants in a study assessing bone-implant contact in rabbits (246).

Anti-vascular endothelial growth factor (Anti-VEGF): Post-operative anti-VEGF (4 μg/kg, IP) was found to impair osseointegration of cylindrical titanium implants in one study assessing bone-implant contact and peri-implant bone formation in rats (247).

Ranibizumab: Post-operative intraperitoneal administration of ranibizumab (15 μg/kg) was found to impair osseointegration of cylindrical titanium implants in one study assessing bone-to-implant contact and peri-implant bone formation in rats (247).

Bevacizumab: Post-operative intraperitoneal administration of bevacizumab (15 μg/kg, IP) was found to impair osseointegration of cylindrical titanium implants in one study assessing bone-implant contact and peri-implant bone formation in rabbits (296).

Antibiotics

In 3 randomized controlled clinical trials (248-250) and a retrospective cohort study (251) pre-operative administration of antibiotics had no significant effect on implant failure. Moreover, a study on rats showed that pre-operative (40mg/kg) and post-operative (10 mg/kg at day 3, 5, and 7) amoxicillin impaired osseointegration (252), while postoperative oral administration of doxycycline (16.67 mg/kg) enhanced bone-implant contact in diabetic rats (253).

Anti-Diabetic

Insulin: In animal studies, different doses of insulin have been assessed for their impact on implant osseointegration. Insulin doses of 2-17 IU/day were found to enhance osseointegration in eight different studies on diabetic rats (171, 254-259, 302). Four of these studies used screw-form implants, two used cylindrical implants, one used rod-shaped implants, and one used dental titanium implants. These studies showed that insulin improved bone-to-implant contact, and pull-out test, and the bone area within the limits of the implant threads. Also, combining insulin with vitamin D (12 μg/kg/daily, gavage) resulted in improved BIO in one study on diabetic rats (171). On the other hand, one study on diabetic rabbits using 20 IU/day did not show any significant effect on the osteointegration of unthreaded titanium implants in terms of bone-implant contact and removal torque (260). In addition, combining insulin (12 IU/kg, SC) with cinaciguat (10 mg/kg/day, Intraperitoneal) improved BIO in one study on diabetic rats (302).

Metformin: Different doses of metformin have been assessed for their impact on bone-implant osseointegration in three studies on rats. Short term use of oral metformin (40 and 100 mg/kg/daily) was found to enhance osseointegration in two of these studies (261, 262), while long term use of oral metformin (40 mg/kg/daily) showed a negative effect on osseointegration in the third study (262). All three studies used screw-form titanium implants. The studies on short term use of oral metformin showed improve in bone-to-implant contact and peri-implant bone area, while the long term used of oral metformin impaired bone-to-implant contact, and peri-implant bone area.

Aminoguanidine: Intraperitoneally administration of aminoguanidine (10-132.2 mg/kg/daily) was found to enhance osseointegration of screw-form titanium implants and cylindrical titanium implants in 2 studies assessing bone- implant contact and counter-torque in rats (253, 263).

Sitagliptin: Post-operative orally administration of sitagliptin (10 mg/kg/day) did not reverse the negative effects of type I diabetic rats on osseointegration in this study (299). This study used screw-form titanium implants and showed that sitagliptin didn't improve the bone-to-implant contact and bone marrow to implant contact.

Cinaciguat: Post-operative administration of cinaciguat (7 μg/kg, IP) enhanced osseointegration of screw-form titanium implants in a study assessing bone-to-implant contact and pull-out test in diabetic rats (302).

Antihypertensive drugs*:* Systemic administration of unspecified antihypertensives was associated with an increased survival rate of osseointegrated implants in one retrospective cohort study (264). Also, hypertension drugs such as propranolol and nifedipine have been assessed in vivo.

Propranolol: Post-operative administration of propranolol (5 mg/kg/day, SC) enhanced BIO of cylindrical titanium implants in a study assessing bone-implant contact in rats (265).

Nifedipine: Post-operative administration of nifedipine (50 mg/kg/day, SC) combined with the immunosuppressant CsA(10 mg/kg/daily) had no significant effect on osseointegration of screw-shaped titanium implants in two studies assessing peri-implant bone density in rabbits (266)(279).

Statins

In a retrospective cohort study on total hip arthroplasty use of statins was associated with significantly increased 5 years survival of the implants (267). In animal studies, post-operative administration of simvastatin (3-10 or 25-50 mg/kg, SC, IP or Oral) enhanced osseointegration in eight animal studies (268) (161, 162, 269-273, 303). Four were on ovariectomized rats, two on non-ovariectomized rats, one on low protein diet rats, one on dogs, and one on rabbits. Seven of these studies used titanium implants (3 screw-shaped, 2 unspecified design, 2 hydroxyapatite-coated, 1 cylindrical), and one used grit-blasted implants. These studies analyzed bone-to-implant contact, the bone area within the limits of implant threads, peri-implant bone quality, bone density, pull-out test, and push-out force. Moreover, a study on ovariectomized rats and another one on rats showed that combined administration of simvastatin (5 and 25 mg/kg/daily) with parathyroid hormone replacement therapy (60 and 40 μg/kg/three times a week) enhanced osseointegration (161, 162). On the other hand, postoperative oral administration of different doses of simvastatin (5, 10, or 50 mg/kg) was found to have no effect on osseointegration of HA-coated stainless-steel implants in a study assessing bone-implant contact and peri-implant bone density in rats (274).

Blood Drugs

Anti-Hemorrhagic (Aprotinin): Post-operative intravenous administration of aprotinin (7,200 KIU) was found to have no effect on osseointegration of steel Kirschner-wires in one study on rats assessing bone-to-implant contact and push-out force (275).

Anti-Thrombotic (Warfarin): Post-operative oral administration of warfarin (5 mg/kg) was found to impair osseointegration of cylindrical hydroxyapatite-coated cobalt-chromium-molybdenum alloy implants in one study assessing bone-to-implant contact and push-out force analyses in goats (276). However, the hydroxyapatite-coatings reverse the negative effect and improve BIO.

Immunosuppression

Cyclosporin A*:* Pre- and post-operative administration of cyclosporin A (10 mg/kg/daily, SC) was found to impair osseointegration in five animal studies on rabbits (277-281). Four of these studies used screw-shaped titanium implants, and one used cylindrical titanium dental implants. Bone-to-implant contact, the bone area within the limits of the implant threads, peri-implant bone quality and density, and removal torque test analyses showed that cyclosporin A impaired bone-implant osseointegration. On the other hand, post-operative intraperitoneal administration of cyclosporin A (2 mg/kg) was found to have no effect on osseointegration of threaded titanium cylindrical chambers in a study assessing bone-to-implant contact and peri-implant bone area in rats (282). Moreover, Post-operative subcutaneous administration of cyclosporin A (10 mg/kg/day) in combination with nifedipine (50 mg/kg/day) and antihypertension medications were found to have no effect on osseointegration in a study on rabbits (266)(279).

FK-506*:* Pre- and post-operative subcutaneous administration of FK-506 (1 mg/kg) was found to impair osseointegration of sand-blasted titanium implants in a study assessing bone-implant contact and peri-implant bone formation in rats (283).

Anti-Gastric

Proton Pump Inhibitors (PPI)*:* Systemic administration of PPIs was associated with high risk of implant failure in two retrospective cohort studies (284, 285). Also, post-operative administration of PPIs (5 mg/kg/daily, IP) was found to impair osseointegration of titanium implants in a study assessing bone-implant contact and peri-implant bone formation in rats (286).

Hyperbaric oxygen (HBO)

Post-operative systemic administration of HBO (10 sessions, 2.0-2.5 ATM of pure oxygen, 90 minutes/day) enhanced early osseoin-

tegration of screw-shaped titanium implants in three animal studies, one on diabetic rabbits and two on diabetic rats (287, 288, 294). On the other hand, one study showed that HBO (10 sessions, 2.80 ATM of pure oxygen, 120 minutes/twice a day) had no effect on BIO of screw-shaped titanium implant in irradiated rats (289).

Discussion

This study achieved two key objectives, it provided an innovated way of performing systematic evidence mappings using AI, and it provided a comprehensive systematic mapping of the medications known to affect osseointegration. The results of this study highlighted the importance of using AI in data screening for evidence mapping reviews. Using machine learning, we were able to automatically screen 599,604 articles by only having to screen manually 1.49 % of the total dataset. This allowed us to retrieve 281 relevant articles and reduced the workload of the evidence mapping by 95% while achieving high sensitivity, specificity, and accuracy. As a result of this, we were able to identify a total of 31 drug categories known to affect osseointegration.

The literature on the use of AI for systematic mappings is scarce, and so far, we are only aware of two groups that have done this. A study from Lam, J. et al., on the effect of low-calorie sweeteners (LCS) on health outcomes (16), and the tool of Tripdatabase.com for fully automated mapping that does not require any manual screening by the user (17). Our method required a lower percentage of manual article screening than Lam, J. et al. (1.49% vs. 28%), and it was able to detect far more relevant articles than Tripdatabase.com. Also, Tripdatabase.com can only perform automated evidence synthesis for RCT and SR, and it cannot identify and synthesize observational or animal studies (17). To compare our systematic mapping with the performance of Tripdatabase.com, on November 18, 2019, we executed a search for the term “osseointegration” on the evidence map tool of Tripdatabase.com. The search on the Tripdatabase.com was only able to detect 2 RCTs assessing osseointegration pharmacology. This is way below the 26 RCTs detected with our method. Also, within the limits of our knowledge, unlike the studies of Lam, J. et al., and the Tripdatabase.com, our algorithm for systematic mapping is the first that has been validated against published systematic reviews performed by humans (16, 17).

Our algorithm was validated against 2 already published systematic reviews with search strategies that fall within the scope of ours (29) (291). We validated our algorithm only against the RCTs and observational clinical studies included by Chappuis et al., because in our review we excluded cross-section, case-series and case reports. Therefore, we only focused on 14 of the 17 articles included in their review for our validation. We used our algorithm to screen the 596 articles identified by the search strategy of their published systematic review, and our AI was able to identify 13 of the 14 articles included by the authors that met our inclusion criteria. This indicated that our AI could have missed up to 7% of relevant clinical studies. Nevertheless, our review included 77 more clinical studies (five-folds) compared to Chappuis et al. article (29) including 28 RCTs compared to 2 articles identified by Chappuis et al., and 49 observational studies compared to 12 articles identified by Chappuis et al. (29). Also, we were able to identify 14 drug classes assessed in clinical studies compared to 5 drug classes identified by Chappuis et al. (29). Upon validation with the systematic review of Aghaloo et al. (291), our AI was able to identify 14 of the 15 articles retrieved by Aghaloo et al that fit our inclusion criteria reaching a sensitivity of 93%.

The thirty-one drug classes identified by our systematic mapping are known to affect different metabolic pathways involved in the bone healing. For instance, Warfarin, NSAID, and Aspirin are known to impair hemostasis, and they were found to impair osseointegration. Cannabis, NSAID, Aspirin, Corticosteroids, Antibiotics, Alcohol, Metformin, and Immunosuppressants affect the inflammation. Chemotherapy, Nicotine, Alcohol, Corticosteroids, Cannabis, Hyperbaric oxygen, Aprotinin, Melatonin, Parathyroid hormone replacement, and Anti-VEGF affect angiogenesis and proliferation. And the following drugs are known to affect remodeling: Chemotherapy, Corticosteroids, Antibiotics, Prostaglandin EP4 receptor agonist, Anti-Sclerostin antibody, Statin, PPI, Lithium chloride, SSRIs, Vitamin D, Oxytocin, Anti-RANKL, Estradiol, Dihydrotestosterone, Thyroid hormone replacement, Parathyroid hormone replacement, Insulin, Melatonin, NSAID, Antihypertensive, Bisphosphonate, Raloxifene, Strontium ranelate, and Glucocorticoids (Figure 5). These observations confirm our hypothesis that drugs affecting the bone healing pathways could affect osseointegration (34-290). Our method for screening the literature could be used for identifying the side effects of medications on other medical devices.

Craniofacial and skeletal bones have different embryological origins and metabolism. Thus, drugs and osseointegrated implants could behave differently in these two types of bone. Among the 12 drugs assessed for their effect on implant osseointegration in both craniofacial and skeletal bones, most had similar effects on both types of bone. This included Zoledronic Acid, Alendronate, Ibuprofen, 17β estradiol, Alcohol, Anti-Hypertensive, and PTH (Figure 6). However, Diclofenac sodium, Prednisolone, Amoxicillin and Chemotherapy impaired the osseointegration of ortho-

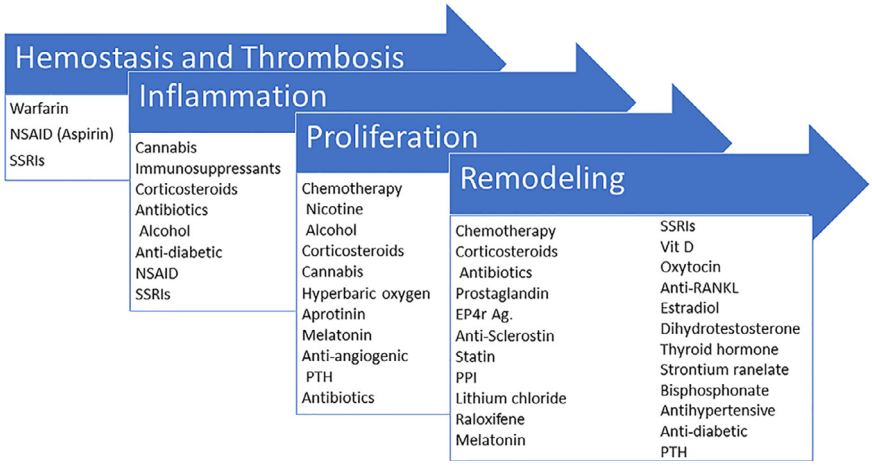

Figure 5. The stages of osseointegration that could be affected by the drugs identified in our review (34-290).

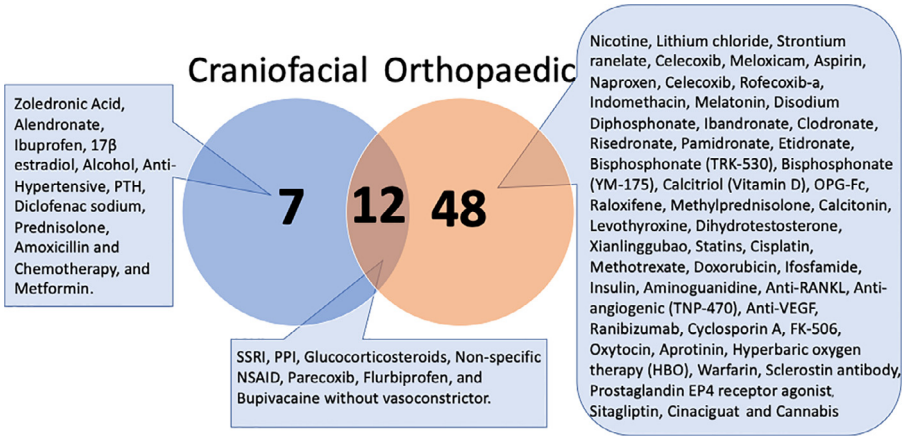

Figure 6. Venn diagram showing the number of drugs that were tested in each type of bone, and the list of the drugs that were tested in each type of bone.

pedic implants (186, 187, 238, 240), but did not show a significant effect on craniofacial implants (188, 189, 238, 241) (248-252). On the other hand, metformin was found to have a positive effect on orthopedic implants (261), and a negative effect on craniofacial implants, (Figure 6) (262).

Few drugs were assessed only in craniofacial bones. This included SSRI, PPI, Glucocorticosteroids, Non-specific NSAID, Parecoxib, Flurbiprofen, and Bupivacaine (Figure 6). On the other hand, several drugs were assessed on implants placed only in skeletal bones. This included: Nicotine, Lithium chloride, Strontium ranelate, Celecoxib, Meloxicam, Aspirin, Naproxen, Celecoxib, Rofecoxib-a, Indomethacin, Melatonin, Disodium Diphosphonate, Ibandronate, Clodronate, Risedronate, Pamidronate, Etidronate, Bisphosphonate (TRK-530), Bisphosphonate (YM-175), Calcitriol (Vitamin D), OPG-Fc, Raloxifene, Methylprednisolone, Calcitonin, Levothyroxine, Dihydrotestosterone, Xianling gubao, Statins, Cisplatin, Methotrexate, Doxorubicin, Ifosfamide, Insulin, Aminoguanidine, Anti-RANKL, Anti-angiogenic (TNP-470), Anti-VEGF, Ranibizumab, Cyclosporin A, FK-506, Oxytocin, Aprotinin, Hyperbaric oxygen therapy (HBO), Warfarin, Sclerostin antibody, Prostaglandin EP4 receptor agonist, Sitagliptin, Cinaciguat and Cannabis (Figure 6). Future research should be performed to assess the effect of these drugs on both craniofacial and skeletal implants.

This study assessed both clinical and animal studies to provide a comprehensive overview of the literature. Even though human studies are more relevant for clinical practice, many medications have only been investigated in animals, thus the summarizing them in this review could provide guidance for future clinical studies.

Conclusions

A machine learning MeSH-classifier trained with a dataset including non-similar studies could save up to 98% of the screening required in an evidence mapping review. This allows for evidence mapping reviews addressing complex question such as, “What drugs could affect implant osseointegration?” Our evidence mapping on this subject revealed that osseointegration could be affected by drugs known to affect metabolic activities involved in its process.

Financial support

We acknowledge financial support from McGill Faculty of Dentistry, Jordanian Royal Medical Services, Jazan University College of Dentistry, and the Saudi Arabian Cultural Bureau in Ottawa for support.

Statement of Significance

A significant number of patients treated with osseointegrated medical devices take medications for various reasons, yet the effect of their medications on the surgical treatments is usually unknown for surgeons and patients. This extensive review provides them with a comprehensive summary of all the known effects of drugs on osseointegrated medical devices, and it suggests novel directions for pharmacological research to better understand the role of drugs in orthopedic and craniofacial treatments.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Acknowledgments

We thank Mr. Martin Morris for helping build the search strategy, and The Canada Research Chair program, the Quebec Network for Bone and Oral Health Research (RSBO), Jazan University, College of Dentistry, and the Saudi Arabian Cultural Bureau in Ottawa for their financial support.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.actbio.2020.11.011.

References

[1] S Petis, JL Howard, BL Lanting, EM Vasarhelyi, Surgical approach in primary total hip arthroplasty: anatomy, technique and clinical outcomes, Can J Surg 58 (2) (2015) 128–139.
[2] American Dental Association, Dental Implants (2015, February 12).
[3] L Gaviria, JP Salcido, T Guda, JL Ong, Current trends in dental implants, J Korean Assoc Oral Maxillofac Surg 40 (2) (2014) 50–60.
[4] ML Carlson, BP O'Connell, CM Lohse, CL Driscoll, AD Sweeney, Survey of the American Neurotology Society on Cochlear Implantation: Part 2, Surgical and Device-Related Practice Patterns, Otol Neurotol 39 (1) (2018) e20–ee7.
[5] P Vaidya, S Mahale, S Kale, A Patil, M Sciences, Osseointegration—a review, IOSR Journal 16 (1) (2017) 45–48.
[6] X Wu, F. Tamimi, Pharmacological Risk Assessment for Dental Implants, in: E Emami, J Feine (Eds.), Mandibular Implant Prostheses: Guidelines for Edentulous Geriatric Populations, Cham: Springer International Publishing, 2018, pp. 37–65.

[7] RP Szumita, Szumita PM. S214, Hemostasis: A Clinical Review of Pathophysiology, Pharmacotherapy, and Perioperative Management, J. Oral Maxillofac. Surg. 65 (9) (2007) 88–89.
[8] IM Miake-Lye, S Hempel, R Shanman, PG Shekelle, What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products, Syst Rev 5 (1) (2016) 28.
[9] WJ Sutherland, CFR Wordley, A fresh approach to evidence synthesis, Nature 558 (7710) (2018) 364–366.
[10] A Gates, C Johnson, L Hartling, Technology-assisted title and abstract screening for systematic reviews: a retrospective evaluation of the Abstrackr machine learning tool, Syst Rev 7 (1) (2018) 45.
[11] G Tsafnat, P Glasziou, MK Choong, A Dunn, F Galgani, E Coiera, Systematic review automation technologies, Syst Rev 3 (1) (2014) 74.
[12] H Waddington, E Masset, E Jimenez, What have we learned after ten years of systematic reviews in international development?, 10, Taylor & Francis; J Dev Effect, 2018.
[13] A Bannach-Brown, P Przybyla, J Thomas, ASC Rice, S Ananiadou, J Liao, Machine learning algorithms for systematic review: reducing workload in a preclinical review of animal studies and reducing human screening error, Syst Rev 8 (1) (2019) 23.
[14] G Tsafnat, P Glasziou, G Karystianis, E Coiera, Automated screening of research studies for systematic reviews using study characteristics, Syst Rev 7 (1) (2018) 64.
[15] A O'Mara-Eves, J Thomas, J McNaught, M Miwa, S Ananiadou, Using text mining for study identification in systematic reviews: a systematic review of current approaches, Syst Rev 4 (2015) 5.
[16] J Lam, BE Howard, K Thayer, RR Shah, Low-calorie sweeteners and health outcomes: A demonstration of rapid evidence mapping (rEM), Environ Int 123 (2019) 451–458.
[17] J Brassey, C Price, J Edwards, M Zlabinger, A Bampoulidis, A Hanbury, Developing a fully automated evidence synthesis tool for identifying, assessing and collating the evidence, BMJ Evid Based Med (2019) bmjebm-2018-111126.
[18] DJ Berndt, JA McCart, DK Finch, Luther SLJAToMIS, A case study of data quality in text mining clinical progress notes, ACM Trans. Manage. Inf. Syst. 6 (1) (2015) 1–21.
[19] C Friedman, TC Rindflesch, M Corn, Natural language processing: state of the art and prospects for significant progress, a workshop sponsored by the National Library of Medicine, J Biomed Inform 46 (5) (2013) 765–773.
[20] Z Yu, E Bernstam, T Cohen, BC Wallace, TR Johnson, Improving the utility of MeSH® terms using the TopicalMeSH representation, J Biomed Inform 61 (2016) 77–86.
[21] AC ricco, E Lillie, W Zarin, KK O'Brien, H Colquhoun, D Levac, D Moher, MDJ Peters, T Horsley, L Weeks, S Hempel, EA Akl, C Chang, J McGowan, L Stewart, L Hartling, A Aldcroft, MG Wilson, C Garritty, S Lewin, CM Godfrey, MT Macdonald, EV Langlois, K Soares-Weiser, J Moriarty, T Clifford, Tunçalp Ö, SE Straus, PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation, Ann. Intern. Med. 169 (7) (2018) 467–473.
[22] P Bragge, O Clavisi, T Turner, E Tavender, A Collie, RL Gruen, The global evidence mapping initiative: scoping research in broad topic areas, BMC Med Res Methodol 11 (1) (2011) 92.
[23] M Ballesteros, N Montero, A López-Pousa, G Urrútia, I Solà, G Rada, H Pardo-Hernandez, X Bonfill, Evidence mapping based on systematic reviews of therapeutic interventions for gastrointestinal stromal tumors (GIST), BMC Med Res Methodol 17 (1) (2017) 135.
[24] MAH Eibe Frank, H Ian, Witten. The WEKA Workbench. Online Appendix for "Data Mining: Practical Machine Learning Tools and Techniques", Morgan Kaufmann, Fourth Edition (2016).
[25] IH Witten, E Frank, MA Hall, CJ Pal, Data Mining: Practical machine learning tools and techniques, Morgan Kaufmann, 2016.
[26] C-L Huang, M-C Chen, C-J Wang, Credit scoring with a data mining approach based on support vector machines, Expert Syst Appl 33 (4) (2007) 847–856.
[27] S Jaspers, E De Troyer, MJESP Aerts, Machine learning techniques for the automation of literature reviews and systematic reviews in EFSA, EFSA 15 (6) (2018) 1427E.
[28] P Przybyła, AJ Brockmeier, G Kontonatsios, MA Le Pogam, J McNaught, E von Elm, K Nolan, S Ananiadou, Prioritising references for systematic reviews with RobotAnalyst: A user study, Res Synth Methods 9 (3) (2018) 470–488.
[29] V Chappuis, G Avila-Ortiz, MG Araújo, A Monje, Medication-related dental implant failure: Systematic review and meta-analysis, Clin Oral Implant Res 29 (2018) 55–68.
[30] HJ Schünemann, AD Oxman, JP Higgins, GE Vist, P Glasziou, G Guyatt, Chapter 5: Defining the review question and developing criteria for including studies, in: PTH Julian, G. Sally (Eds.), Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0, 5, eds, Great Britain, 2008, pp. 84–90.
[31] CR Hooijmans, MM Rovers, RB de Vries, M Leenaars, M Ritskes-Hoitinga, MW Langendam, SYRCLE's risk of bias tool for animal studies, BMC Med Res Methodol 14 (2014) 43.
[32] X Zeng, Y Zhang, JS Kwong, C Zhang, S Li, F Sun, Y Niu, L Du, The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review, J Evid Based Med 8 (1) (2015) 2–10.
[33] E von Elm, DG Altman, M Egger, SJ Pocock, PC Gotzsche, JP Vandenbroucke, The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies, Int J Surg 12 (12) (2014) 1495–1499.
[34] D Prieto-Alhambra, MK Javaid, A Judge, D Murray, A Carr, C Cooper, Arden NK Association between bisphosphonate use and implant survival after primary total arthroplasty of the knee or hip: population based retrospective cohort study, BMJ (Clinical research ed) 343 (2011) d7222.
[35] S-H Fu, C-Y Wang, R-S Yang, F-L Wu, F-Y Hsiao, Bisphosphonate use and the risk of undergoing total knee arthroplasty in osteoporotic patients with osteoarthritis: a nationwide cohort study in taiwan, J Bone Joint Surg Am 99 (11) (2017) 938–946.
[36] D Prieto-Alhambra, A Lalmohamed, B Abrahamsen, NK Arden, A de Boer, P Vestergaard, F de Vries, Oral bisphosphonate use and total knee/hip implant survival: validation of results in an external population-based cohort, Arthritis Rheumatol 66 (11) (2014) 3233–3240.
[37] PG Cho, GY Ji, DA Shin, Y Ha, K Kim, An effect comparison of teriparatide and bisphosphonate on posterior lumbar interbody fusion in patients with osteoporosis: a prospective cohort study and preliminary data, Eur Spine J 26 (3) (2017) 691–697.
[38] JK Yip, LN Borrell, SC Cho, H Francisco, DP Tarnow, Association between oral bisphosphonate use and dental implant failure among middle-aged women, J Clin Periodontol 39 (4) (2012) 408–414.
[39] S Memon, RL Weltman, JA Katancik, Oral bisphosphonates: early endosseous dental implant success and crestal bone changes, A retrospective study. Int J Oral Maxillofac Implants. 27 (5) (2012) 1216–1222.
[40] BT Grant, C Amenedo, K Freeman, RA Kraut, Outcomes of placing dental implants in patients taking oral bisphosphonates: a review of 115 cases, J Oral Maxillofac Surg 66 (2) (2008) 223–230.
[41] M Mozzati, V Arata, M Giacomello, M Del Fabbro, G Gallesio, C Mortellaro, L Bergamasco, Failure risk estimates after dental implants placement associated with plasma rich in growth factor-Endoret in osteoporotic women under bisphosphonate therapy, J Craniofac Surg 26 (3) (2015) 749–755.
[42] BM Bell, RE Bell, Oral bisphosphonates and dental implants: a retrospective study, J Oral Maxillofac Surg 66 (5) (2008) 1022–1024.
[43] P Famili, S Quigley, T Mosher, Survival of dental implants among post–menopausal female dental school patients taking oral bisphosphonates: a retrospective study, Compend Contin Educ Dent 32 (6) (2011) E106–E109.
[44] TM Zahid, BY Wang, RE Cohen, Influence of bisphosphonates on alveolar bone loss around osseointegrated implants, J Oral Implantol 37 (3) (2011) 335–346.
[45] DF Scott, JN Woltz, RR Smith, Effect of zoledronic acid on reducing femoral bone mineral density loss following total hip arthroplasty: preliminary results of a prospective randomized trial, J Arthroplasty 28 (4) (2013) 671–675.
[46] G Friedl, R Radl, C Stihsen, P Rehak, R Aigner, R Windhager, The effect of a single infusion of zoledronic acid on early implant migration in total hip arthroplasty: a randomized, double-blind, controlled trial, J Bone Joint Surg Am 91 (2) (2009) 274–281.
[47] TW Huang, CJ Wang, HN Shih, Y Chang, KC Huang, KT Peng, MS Lee, Bone turnover and periprosthetic bone loss after cementless total hip arthroplasty can be restored by zoledronic acid: a prospective, randomized, open-label, controlled trial, BMC musculoskeletal disorders 18 (1) (2017) 209.
[48] T Siebert, R Jurkovic, D Statelova, J Strecha, Immediate Implant Placement in a Patient With Osteoporosis Undergoing Bisphosphonate Therapy: 1-Year Preliminary Prospective Study, J Oral Implantol 41 (2015) Spec No:360-5.
[49] B Chen, Y Li, X Yang, H Xu, D Xie, Zoledronic acid enhances bone-implant osseointegration more than alendronate and strontium ranelate in ovariectomized rats, Osteoporos Int 24 (7) (2013) 2115–2121.
[50] F Yaman, S Ağaçayak, S Atilgan, E Benlidayi, MC Ucan, B Erol, B Kaya, A Gunay, S Guven, Effects of systemic zoledronic Acid administration on osseointegration of hydroxyapatite-coated and resorbable blast material surface implants in rabbit models, Int J Oral Maxillofac Implants 27 (6) (2012) 1443–1447.
[51] JP Li, P Li, J Hu, W Dong, NN Liao, MC Qi, JY Li, Early healing of hydroxyapatite-coated implants in grafted bone of zoledronic acid-treated osteoporotic rabbits, J Periodontol 85 (2) (2014) 308–316.
[52] E Dikicier, U Karacayli, S Dikicier, Y Gunaydin, Effect of systemic administered zoledronic acid on osseointegration of a titanium implant in ovariectomized rats, J Craniomaxillofac Surg 42 (7) (2014) 1106–1111.
[53] S Dikicier, E Dikicier, U Karacayli, B Erguder, Radiodensitometric study for evaluation of bone mineral density around dental implants after zoledronic acid treatment in ovariectomized rats, Med Oral Patol Oral Cir Bucal 22 (3) (2017) e377–ee82.
[54] JD Bobyn, SA Hacking, JJ Krygier, EJ Harvey, DG Little, M Tanzer, Zoledronic acid causes enhancement of bone growth into porous implants, J Bone Joint Surg Br 87 (3) (2005) 416–420.
[55] M Qi, J Hu, J Li, J Li, W Dong, X Feng, J Yu, Effect of zoledronate acid treatment on osseointegration and fixation of implants in autologous iliac bone grafts in ovariectomized rabbits, Bone 50 (1) (2012) 119–127.
[56] S Dundar, F Yaman, O Gecor, O Cakmak, M Kirtay, TT Yildirim, T Karaman, ME Benlidayi, Effects of local and systemic zoledronic acid application on titanium implant osseointegration: an experimental study conducted on two surface types, J Craniofac Surg 28 (4) (2017) 935–938.
[57] M Ayan, D Dolanmaz, A Mihmanli, A Ayan, M Kurkcu, The effect of systemically administrated zoledronic acid on the osseointegration of dental implants, Oral Dis 18 (8) (2012) 802–808.
[58] J Blazsek, C Dobó Nagy, I Blazsek, R Varga, B Vecsei, P Fejérdy, G Varga, Aminobisphosphonate stimulates bone regeneration and enforces consolidation of titanium implant into a new rat caudal vertebrae model, Pathol Oncol Res 15 (4) (2009) 567–577.

[59] AE Goodship, GW Blunn, J Green, MJ Coathup, Prevention of strain-related osteopenia in aseptic loosening of hip prostheses using perioperative bisphosphonate, J Orthop Res 26 (5) (2008) 693–703.
[60] YF Li, XD Li, CY Bao, QM Chen, H Zhang, J Hu, Promotion of peri-implant bone healing by systemically administered parathyroid hormone (1-34) and zoledronic acid adsorbed onto the implant surface, Osteoporos Int: 24 (3) (2013) 1063–1071.
[61] FQ Wu, J Ye, LG Wu, [Inhibitory effect of zoledronate sodium on periprosthetic osteolysis induced by polyethylene particles], Zhongguo Gu Shang 28 (10) (2015) 936–939.
[62] G Spence, S Phillips, C Campion, R Brooks, N Rushton, Bone formation in a carbonate-substituted hydroxyapatite implant is inhibited by zoledronate: the importance of bioresorption to osteoconduction, J Bone Joint Surg Br 90 (12) (2008) 1635–1640.
[63] SS Huja, B Kaya, X Mo, AM D'Atri, SA Fernandez, Effect of zoledronic acid on bone healing subsequent to mini-implant insertion, Angle Orthod 81 (3) (2011) 363–369.
[64] SS Huja, A Mason, CE Fenell, X Mo, S Hueni, AM D'Atri, SA Fernandez, Effects of short-term zoledronic acid treatment on bone remodeling and healing at surgical sites in the maxilla and mandible of aged dogs, J Oral Maxillofac Surg 69 (2) (2011) 418–427.
[65] I Kim, H Ki, W Lee, H Kim, JB Park, The effect of systemically administered bisphosphonates on bony healing after tooth extraction and osseointegration of dental implants in the rabbit maxilla, Int J Oral Maxillofac Implants 28 (5) (2013) 1194–1200.
[66] A Yildiz, E Esen, M Kurkcu, I Damlar, K Daglioglu, T Akova, Effect of zoledronic acid on osseointegration of titanium implants: an experimental study in an ovariectomized rabbit model, J Oral Maxillofac Surg 68 (3) (2010) 515–523.
[67] MA de Oliveira, DA Asahi, CA Silveira, LAP Lima, M Glick, Gallottini MJCoir, The effects of zoledronic acid and dexamethasone on osseointegration of endosseous implants: histological and histomorphometrical evaluation in rats, Clin Oral Implants Res 26 (4) (2015) e17–e21.
[68] JS Carvas, RM Pereira, VF Caparbo, P Fuller, CA Silveira, LA Lima, E Bonfa, SB Mello, A single dose of zoledronic acid reverses the deleterious effects of glucocorticoids on titanium implant osseointegration, Osteoporos Int 21 (10) (2010) 1723–1729.
[69] J Lee, C Lee, C Choi, QCT bone mineral density responses to 1 year of oral bisphosphonate after total knee replacement for knee osteoarthritis, Osteoporos Int 24 (1) (2013) 287–292.
[70] T Hennigs, M Arabmotlagh, A Schwarz, L Zichner, [Dose-dependent prevention of early periprosthetic bone loss by alendronate], Z Orthop Ihre Grenzgeb 140 (1) (2002) 42–47.
[71] JK Lee, CH Choi, CN Kang, Quantitative computed tomography assessment of bone mineral density after 2 years' oral bisphosphonate treatment in postmenopausal osteoarthritis patients who underwent total knee arthroplasty, J Int Med Res 41 (3) (2013) 878–888.
[72] P Kinov, P Tivchev, P Doukova, A Leithner, Effect of risedronate on bone metabolism after total hip arthroplasty: a prospective randomised study, Acta orthopaedica Belgica 72 (1) (2006) 44–50.
[73] AV Jaroma, TA Soininvaara, H Kroger, Effect of one-year post-operative alendronate treatment on periprosthetic bone after total knee arthroplasty. A seven-year randomised controlled trial of 26 patients, Bone Joint J 97-b (3) (2015) 337–345.
[74] N Iwamoto, Y Inaba, N Kobayashi, T Ishida, Y Yukizawa, TJ Saito, A comparison of the effects of alendronate and alfacalcidol on bone mineral density around the femoral implant and in the lumbar spine after total hip arthroplasty, J Bone Joint Surg Am 93 (13) (2011) 1203–1209.
[75] T Tapaninen, P Venesmaa, J Jurvelin, H Miettinen, Kröger HJSJoS, Alendronate reduces periprosthetic bone loss after uncemented primary total hip arthroplasty—a 5-year follow-up of 16 patients, Scand J Surg 99 (1) (2010) 32–37.
[76] T Nishioka, S Yagi, T Mitsuhashi, M Miyamoto, T Tamura, T Kobayashi, T Enishi, Alendronate inhibits periprosthetic bone loss around uncemented femoral components 25 (3) (2007) 179–183.
[77] A Moroni, C Faldini, A Hoang-Kim, F Pegreffi, SJJ Giannini, Alendronate improves screw fixation in osteoporotic bone, J Bone Joint Surg Am 89 (1) (2007) 96–101.
[78] CJ Wang, JW Wang, LH Weng, CC Hsu, CC Huang, HS Chen, The effect of alendronate on bone mineral density in the distal part of the femur and proximal part of the tibia after total knee arthroplasty, J Bone Joint Surg Am 85-a (11) (2003) 2121–2126.
[79] TA Soininvaara, JS Jurvelin, HJ Miettinen, OT Suomalainen, EM Alhava, PJ Kroger, Effect of alendronate on periprosthetic bone loss after total knee arthroplasty: a one-year, randomized, controlled trial of 19 patients, Calcif Tissue Int 71 (6) (2002) 472–477.
[80] M Arabmotlagh, M Pilz, J Warzecha, Rauschmann MJJoOR, Changes of femoral periprosthetic bone mineral density 6 years after treatment with alendronate following total hip arthroplasty, J Orthop Res 27 (2) (2009) 183–188.
[81] N Kobayashi, Y Inaba, M Uchiyama, H Ike, S Kubota, T Saito, Teriparatide Versus Alendronate for the Preservation of Bone Mineral Density After Total Hip Arthroplasty - A randomized Controlled Trial, J Arthroplasty 31 (1) (2016) 333–338.
[82] Y Yukizawa, Y Inaba, N Kobayashi, H Choe, S Kubota, T Saito, Efficacy of Alendronate for the Prevention of Bone Loss in Calcar Region Following Total Hip Arthroplasty, J Arthroplasty 32 (7) (2017) 2176–2180.
[83] W-P Ji, X-L Wang, M-Q Ma, J Lan, H Li, Traumatology. Prevention of early bone loss around the prosthesis by administration of anti-osteoporotic agents and influences of collared and non-collared femoral stem prostheses on early periprosthetic bone loss, Eur J Orthop Surg Traumatol 23 (5) (2013) 565–571.
[84] T Kasai, MA Pogrel, M Hossaini, The prognosis for dental implants placed in patients taking oral bisphosphonates, J Calif Dent Assoc 37 (1) (2009) 39–42.
[85] DC Martin, FS O'Ryan, AT Indresano, P Bogdanos, B Wang, RL Hui, JC Lo, Characteristics of implant failures in patients with a history of oral bisphosphonate therapy, J Oral Maxillofac Surg 68 (3) (2010) 508–514.
[86] U Hansson, S Toksvig-Larsen, L Ryd, Aspenberg PJAo, Once-weekly oral medication with alendronate does not prevent migration of knee prostheses: A double-blind randomized RSA study, Acta Orthop 80 (1) (2009) 41–45.
[87] C-J Wang, J-W Wang, Ko J-y, L-H Weng, C-C Huang, Three-year changes in bone mineral density around the knee after a six-month course of oral alendronate following total knee arthroplasty: a prospective, randomized study, J Bone Joint Surg Am 88 (2) (2006) 267–272.
[88] PA Fugazzotto, WS Lightfoot, R Jaffin, A Kumar, Implant placement with or without simultaneous tooth extraction in patients taking oral bisphosphonates: postoperative healing, early follow-up, and the incidence of complications in two private practices, J Periodontol 78 (9) (2007) 1664–1669.
[89] S Koka, NM Babu, A Norell, Survival of dental implants in post-menopausal bisphosphonate users, J Prosthodont Res 54 (3) (2010) 108–111.
[90] MH Verzola, F Frizzera, GJ de Oliveira, RM Pereira, UP Rodrigues-Filho, KO Nonaka, SR Orrico, Effects of the long-term administration of alendronate on the mechanical properties of the basal bone and on osseointegration, Clin Oral Implants Res 26 (12) (2015) 1466–1475.
[91] JH Kim, YB Park, Z Li, JS Shim, HS Moon, HS Jung, MK Chung, Effect of alendronate on healing of extraction sockets and healing around implants, Oral Dis 17 (7) (2011) 705–711.
[92] S Narai, S. Nagahata, Effects of alendronate on the removal torque of implants in rats with induced osteoporosis, Int J Oral Maxillofac Implants 18 (2) (2003) 218–223.
[93] D Oliveira, JS Hassumi, PH Gomes-Ferreira, TO Polo, GR Ferreira, LP Faverani, R Okamoto, Short term sodium alendronate administration improves the peri-implant bone quality in osteoporotic animals, J Appl Oral Sci 25 (1) (2017) 42–52.
[94] YE Viera-Negrón, Ruan W-h, JN Winger, X Hou, MM Sharawy, JL Borke, Effect of ovariectomy and alendronate on implant osseointegration in rat maxillary bone, J Oral Implantol 34 (2) (2008) 76–82.
[95] TB Jensen, JE Bechtold, X Chen, K Soballe, Systemic alendronate treatment improves fixation of press-fit implants: a canine study using nonloaded implants, J Orthop Res 25 (6) (2007) 772–778.
[96] J Åstrand, P. Aspenberg, Reduction of instability-induced bone resorption using bisphosphonates: high doses are needed in rats, Acta Orthop Scand 73 (1) (2002) 24–30.
[97] D Cankaya, Y Tabak, AM Ozturk, MC Gunay, Perioperative alendronate, risedronate, calcitonin and indomethacin treatment alters femoral stem fixation and periprosthetic bone mineral density in ovariectomized rats, J Orthop Sci 20 (4) (2015) 728–733.
[98] Q Xue, H Li, X Zou, M Dalstra, M Lind, FB Christensen, C Bünger, Alendronate treatment improves bone-pedicle screw interface fixation in posterior lateral spine fusion: an experimental study in a porcine model, Int Orthop 34 (3) (2010) 447–451.
[99] N Conte Neto, CR de Andrade, LC Spolidorio, S Planeta Cda, FC Cruz, A de Souza Bastos, E Marcantonio Jr, Effects of chronic stress and alendronate therapy on the osseointegration of titanium implants, Clin Implant Dent Relat Res 16 (5) (2014) 762–771.
[100] HH Hazzaa, G Amin, EA Abo Hager, MA El Shiekh, Influence of alendronate administration regimen on the final outcome of implant osseointegration in an osteoporotic model, J Int Acad Periodontol 16 (1) (2014) 19–30.
[101] CY Li, YM Zhou, L Wang, YQ Li, L Fu, L Gong, [Effect of alendronate sodium on torque-out testing on implant-bone interfaces in estrogen-deficient rabbits with alendronate systemic administration], Hua Xi Kou Qiang Yi Xue Za Zhi 29 (3) (2011) 233–236.
[102] K Søballe, X Chen, T B Jensen, L Kidder, E Bechtold JJAo, Alendronate treatment in the revision setting, with and without controlled implant motion: an experimental study in dogs, Acta Orthop 78 (6) (2007) 800–807.
[103] M Bernhardsson, O Sandberg, P Aspenberg, Anti-RANKL treatment improves screw fixation in cancellous bone in rats, Injury 46 (6) (2015) 990–995.
[104] Y Nakamura, K Hayashi, S Abu-Ali, M Naito, A Fotovati, Effect of preoperative combined treatment with alendronate and calcitriol on fixation of hydroxyapatite-coated implants in ovariectomized rats, J Bone Joint Surg Am 90 (4) (2008) 824–832.
[105] G Ramalho-Ferreira, L Faverani, F Prado, I Garcia Jr, R Okamoto, Raloxifene enhances peri-implant bone healing in osteoporotic rats, Int J Oral Maxillofac Surg 44 (6) (2015) 798–805.
[106] BL Chen, DH Xie, ZM Zheng, W Lu, CY Ning, YQ Li, FB Li, WM Liao, Comparison of the effects of alendronate sodium and calcitonin on bone-prosthesis osseointegration in osteoporotic rats, Osteoporos Int 22 (1) (2011) 265–270.
[107] G Giro, PG Coelho, RMR Pereira, V Jorgetti, E Marcantonio Jr, SR Orrico, The effect of oestrogen and alendronate therapies on postmenopausal bone loss around osseointegrated titanium implants, Clin Oral Implants Res 22 (3) (2011) 259–264.
[108] G Giro, CE Sakakura, D Gonçalves, RM Pereira, E Marcantonio, SR Orrico, Effect of 17β-Estradiol and Alendronate on the Removal Torque of Osseointegrated Titanium Implants in Ovariectomized Rats, J Periodontol 78 (7) (2007) 1316–1321.

[109] G Giro, D Gonçalves, CE Sakakura, RM Pereira, JE Marcantonio, SR Orrico, Influence of estrogen deficiency and its treatment with alendronate and estrogen on bone density around osseointegrated implants: radiographic study in female rats, Oral Med Oral Pathol Oral Radiol Endod 105 (2) (2008) 162–167.
[110] R Skripitz, HR Johansson, SD Ulrich, A Werner, P Aspenberg, Effect of alendronate and intermittent parathyroid hormone on implant fixation in ovariectomized rats, J Orthop Sci 14 (2) (2009) 138–143.
[111] CR Bragdon, AM Doherty, M Jasty, H Rubash, WH Harris, Effect of oral alendronate on net bone ingrowth into canine cementless total hips, J Arthroplasty 20 (2) (2005) 258–263.
[112] PJ Thadani, B Waxman, E Sladek, R Barmada, MH Gonzalez, Inhibition of particulate debris-induced osteolysis by alendronate in a rat model, Orthopedics 25 (1) (2002) 59–63.
[113] PJ Millett, MJ Allen, MP Bostrom, Effects of alendronate on particle-induced osteolysis in a rat model, J Bone Joint Surg Am 84 (2) (2002) 236–249.
[114] T Miyaji, T Nakase, Y Azuma, N Shimizu, Y Uchiyama, H Yoshikawa, Alendronate inhibits bone resorption at the bone-screw interface, Clin Orthop Relat Res 430 (2005) 195–201.
[115] KC Oh, W Hwang, YB Park, JH Lee, HS Moon, JH Kim, Effects of Alendronate on Bone Remodeling Around Osseointegrated Implants in Rats, Implant Dent 26 (1) (2017) 46–53.
[116] K Oh, H Moon, J Lee, Y Park, JH Kim, Effects of alendronate on the peri-implant bone in rats, Oral Dis 21 (2) (2015) 248–256.
[117] E Tsetsenekou, T Papadopoulos, D Kalyvas, N Papaioannou, S Tangl, G Watzek, The influence of alendronate on osseointegration of nanotreated dental implants in New Zealand rabbits, Clin Oral Implants Res 23 (6) (2012) 659–666.
[118] GE Chacon, EA Stine, PE Larsen, FM Beck, EA McGlumphy, Effect of alendronate on endosseous implant integration: an in vivo study in rabbits, J Oral Maxillofac Surg 64 (7) (2006) 1005–1009.
[119] SR Frenkel, WL Jaffe, CD Valle, L Jazrawi, S Maurer, A Baitner, K Wright, D Sala, M Hawkins, PE Di Cesare, The effect of alendronate (Fosamax™) and implant surface on bone integration and remodeling in a canine model, J Biomed Mater Res 58 (6) (2001) 645–650.
[120] J Astrand, P Aspenberg, Alendronate did not inhibit instability-induced bone resorption. A study in rats, Acta Orthop Scand 70 (1) (1999) 67–70.
[121] X Wang, AS Shanbhag, HE Rubash, CM Agrawal, Short-term effects of bisphosphonates on the biomechanical properties of canine bone, J Biomed Mater Res 44 (4) (1999) 456–460.
[122] T Kitsugi, T Yamamuro, T Nakamura, M Oka, Influence of disodium (1-hydroxythylidene) diphosphonate on bone ingrowth into porous, titanium fiber-mesh implants, J Arthroplasty 10 (2) (1995) 245–253.
[123] C Eberhardt, B Habermann, S Muller, M Schwarz, F Bauss, AH Kurth, The bisphosphonate ibandronate accelerates osseointegration of hydroxyapatite–coated cementless implants in an animal model, J Orthop Sci 12 (1) (2007) 61–66.
[124] AH Kurth, C Eberhardt, S Muller, M Steinacker, M Schwarz, F Bauss, The bisphosphonate ibandronate improves implant integration in osteopenic ovariectomized rats, Bone 37 (2) (2005) 204–210.
[125] C Eberhardt, M Schwarz, AH Kurth, High dosage treatment of nitrogen-containing bisphosphonate ibandronate is required for osseointegration of cementless metal implants, J Orthop Sci 10 (6) (2005) 622–626.
[126] C Eberhardt, U Stumpf, J Brankamp, M Schwarz, AH Kurth, Osseointegration of cementless implants with different bisphosphonate regimens, Clin Orthop Relat Res 447 (2006) 195–200.
[127] B Skoglund, J Holmertz, P Aspenberg, Systemic and local ibandronate enhance screw fixation, J Orthop Res 22 (5) (2004) 1108–1113.
[128] M Hilding, P Aspenberg, Postoperative clodronate decreases prosthetic migration: 4–year follow-up of a randomized radiostereometric study of 50 total knee patients, Acta Orthop 77 (6) (2006) 912–916.
[129] M Hilding, L Ryd, S Toksvig-Larsen, P Aspenberg, Clodronate prevents prosthetic migration: a randomized radiostereometric study of 50 total knee patients, Acta Orthop Scand 71 (6) (2000) 553–557.
[130] C Trevisan, S Ortolani, P Romano, G Isaia, L Agnese, D Dallari, G Grappiolo, R Cherubini, L Massari, G Bianchi, Decreased periprosthetic bone loss in patients treated with clodronate: a 1-year randomized controlled study, Calcif Tissue Int 86 (6) (2010) 436–446.
[131] OG Skoldenberg, MO Salemyr, HS Boden, TE Ahl, PY Adolphson, The effect of weekly risedronate on periprosthetic bone resorption following total hip arthroplasty: a randomized, double-blind, placebo-controlled trial, J Bone Joint Surg Am 93 (20) (2011) 1857–1864.
[132] S Yamasaki, K Masuhara, K Yamaguchi, T Nakai, T Fuji, Y Seino, Risedronate reduces postoperative bone resorption after cementless total hip arthroplasty, Osteoporos Int 18 (7) (2007) 1009–1015.
[133] S Ohtori, G Inoue, S Orita, K Yamauchi, Y Eguchi, N Ochiai, S Kishida, K Kuniyoshi, Y Aoki, J Nakamura, T Ishikawa, M Miyagi, H Kamoda, M Suzuki, G Kubota, Y Sakuma, Y Oikawa, K Inage, T Sainoh, M Takaso, T Toyone, K Takahashi, Comparison of teriparatide and bisphosphonate treatment to reduce pedicle screw loosening after lumbar spinal fusion surgery in postmenopausal women with osteoporosis from a bone quality perspective, Spine (Phila Pa 1976) 38 (8) (2013) E487–EE92.
[134] O Muren, E Akbarian, M Salemyr, H Bodén, T Eisler, A Stark, O Sköldenberg, No effect of risedronate on femoral periprosthetic bone loss following total hip arthroplasty. A 4-year follow-up of 61 patients in a double-blind, randomized placebo-controlled trial, Acta orthopaedica 86 (5) (2015) 569–574.
[135] JM Wilkinson, I Stockley, NF Peel, AJ Hamer, RA Elson, NA Barrington, R Eastell, Effect of pamidronate in preventing local bone loss after total hip arthroplasty: a randomized, double-blind, controlled trial, J Bone Miner Res 16 (3) (2001) 556–564.
[136] Z Xing, KA Hasty, RA Smith, Administration of pamidronate alters bone-titanium attachment in the presence of endotoxin-coated polyethylene particles, J Biomed Mater Res B Appl Biomater 83 (2) (2007) 354–358.
[137] R Dayer, TC Brennan, R Rizzoli, P Ammann, PTH improves titanium implant fixation more than pamidronate or renutrition in osteopenic rats chronically fed a low protein diet, Osteoporos Int 21 (6) (2010) 957–967.
[138] R Dayer, I Badoud, R Rizzoli, P Ammann, Defective implant osseointegration under protein undernutrition: prevention by PTH or pamidronate, J Bone Miner Res 22 (10) (2007) 1526–1533.
[139] HR Johansson, R Skripitz, PJ Aspenberg, Bisphosphonates can block the deterioration in implant fixation after withdrawal of intermittent doses of parathyroid hormone, J Bone Joint Surg Br 90 (3) (2008) 400–404.
[140] T Shibutani, A Inuduka, I Horiki, Q Luan, Y Iwayama, Bisphosphonate inhibits alveolar bone resorption in experimentally-induced peri-implantitis in dogs, Clin Oral Implants Res 12 (2) (2001) 109–114.
[141] M Iwase, KJ Kim, Y Kobayashi, M Itoh, T Itoh, A novel bisphosphonate inhibits inflammatory bone resorption in a rat osteolysis model with continuous infusion of polyethylene particles, J Orthop Res 20 (3) (2002) 499–505.
[142] Y Tokugawa, T Shirota, K Ohno, A Yamaguchi, Effects of bisphosphonate on bone reaction after placement of titanium implants in tibiae of ovariectomized rats, Int J Oral Maxillofac Implants 18 (1) (2003) 66–74.
[143] SK Fokter, R Komadina, A Repše-Fokter, Effect of etidronate in preventing periprosthetic bone loss following cemented hip arthroplasty: a randomized, double blind, controlled trial, Wien Klin Wochenschr 118 (2) (2006) 23–28.
[144] U Kuchler, ER Luvizuto, S Tangl, G Watzek, R Gruber, Short-term teriparatide delivery and osseointegration: a clinical feasibility study, J Dent Res 90 (8) (2011) 1001–1006.
[145] T Kaneko, T Otani, N Kono, Y Mochizuki, T Mori, N Nango, H Ikegami, Y Musha, Weekly injection of teriparatide for bone ingrowth after cementless total knee arthroplasty, J Orthop Surg (Hong Kong) 24 (1) (2016) 16–21.
[146] G Inoue, M Ueno, T Nakazawa, T Imura, W Saito, K Uchida, S Ohtori, T Toyone, N Takahira, M Takaso, Teriparatide increases the insertional torque of pedicle screws during fusion surgery in patients with postmenopausal osteoporosis, J Neurosurg Spine 21 (3) (2014) 425–431.
[147] T Suzuki, F Sukezaki, T Shibuki, Y Toyoshima, T Nagai, K Inagaki, Teriparatide administration increases periprosthetic bone mineral density after total knee arthroplasty: a prospective study, J Arthroplasty 33 (1) (2018) 79–85.
[148] T Shirota, M Tashiro, K Ohno, A Yamaguchi, Effect of intermittent parathyroid hormone (1-34) treatment on the bone response after placement of titanium implants into the tibia of ovariectomized rats, J Oral Maxillofac Surg 61 (4) (2003) 471–480.
[149] MS Corsini, FN Faraco, AA Castro, T Onuma, WR Sendyk, JA Shibli, Effect of systemic intermittent administration of human parathyroid hormone (rh-PTH[1-34]) on the resistance to reverse torque in rabbit tibiae, J Oral Implantol 34 (6) (2008) 298–302.
[150] H Daugaard, B Elmengaard, T Andreassen, J Bechtold, A Lamberg, K Soballe, Parathyroid hormone treatment increases fixation of orthopedic implants with gap healing: a biomechanical and histomorphometric canine study of porous coated titanium alloy implants in cancellous bone, Calcif Tissue Int 88 (4) (2011) 294–303.
[151] MI Almagro, JA Roman-Blas, M Bellido, S Castaneda, R Cortez, G Herrero-Beaumont, PTH [1-34] enhances bone response around titanium implants in a rabbit model of osteoporosis, Clin Oral Implants Res 24 (9) (2013) 1027–1034.
[152] Y Gabet, R Müller, J Levy, R Dimarchi, M Chorev, I Bab, D Kohavi, Parathyroid hormone 1-34 enhances titanium implant anchorage in low-density trabecular bone: a correlative micro-computed tomographic and biomechanical analysis, Bone 39 (2) (2006) 276–282.
[153] B Mair, S Tangl, J Feierfeil, D Skiba, G Watzek, R Gruber, Age-related efficacy of parathyroid hormone on osseointegration in the rat, Clin Oral Implants Res 20 (4) (2009) 400–405.
[154] H Daugaard, B Elmengaard, TT Andreassen, A Lamberg, JE Bechtold, K Soballe, Systemic intermittent parathyroid hormone treatment improves osseointegration of press-fit inserted implants in cancellous bone, Acta orthopaedica 83 (4) (2012) 411–419.
[155] H Daugaard, B Elmengaard, T Andreassen, J Baas, JE Bechtold, K Soballe, The combined effect of parathyroid hormone and bone graft on implant fixation, J Bone Joint Surg Br 93 (1) (2011) 131–139.
[156] ZS Tao, WS Zhou, Z Qiang, KK Tu, ZL Huang, HM Xu, T Sun, YX Lv, W Cui, L Yang, Intermittent administration of human parathyroid hormone (1–34) increases fixation of strontium-doped hydroxyapatite coating titanium implants via electrochemical deposition in ovariectomized rat femur, J Biomater Appl 30 (7) (2016) 952–960.
[157] A Fahlgren, X Yang, C Ciani, JA Ryan, N Kelly, FC Ko, MC van der Meulen, MP Bostrom, The effects of PTH, loading and surgical insult on cancellous bone at the bone-implant interface in the rabbit, Bone 52 (2) (2013) 718–724.
[158] HA Heo, SH Park, YS Jeon, SW Pyo, Enhancing Effect of Intermittent Parathyroid Hormone Administration on Bone Formation After Titanium Implant Placement in an Ovariectomized Rat Maxilla, Implant Dent 25 (2) (2016) 227–231.
[159] X Yang, BF Ricciardi, A Dvorzhinskiy, C Brial, Z Lane, S Bhimani, JC Burket, B Hu, AM Sarkisian, FP Ross, MC van der Meulen, MP Bostrom, Intermittent Parathyroid Hormone Enhances Cancellous Osseointegration of a Novel Murine Tibial Implant, J Bone Joint Surg Am 97 (13) (2015) 1074–1083.

[160] R Skripitz, P. Aspenberg, Implant fixation enhanced by intermittent treatment with parathyroid hormone, J Bone Joint Surg Br 83 (3) (2001) 437–440.
[161] ZS Tao, WS Zhou, KK Tu, ZL Huang, Q Zhou, T Sun, YX Lv, W Cui, L Yang, The effects of combined human parathyroid hormone (1-34) and simvastatin treatment on osseous integration of hydroxyapatite-coated titanium implants in the femur of ovariectomized rats, Injury 46 (11) (2015) 2164–2169.
[162] ZS Tao, WS Zhou, BL Bai, W Cui, YX Lv, XB Yu, ZL Huang, KK Tu, Q Zhou, T Sun, H Li, L Yang, The effects of combined human parathyroid hormone (1-34) and simvastatin treatment on the interface of hydroxyapatite-coated titanium rods implanted into osteopenic rats femurs, J Mater Sci Mater Med 27 (3) (2016) 43.
[163] Y Oki, K Doi, Y Makihara, R Kobatake, T Kubo, K Tsuga, Effects of continual intermittent administration of parathyroid hormone on implant stability in the presence of osteoporosis: an in vivo study using resonance frequency analysis in a rabbit model, J Appl Oral Sci: revista FOB 25 (5) (2017) 498–505.
[164] LL Lima, JB Cesar Neto, EG Cayana, FH Nociti Jr., EA Sallum, MZ Casati, Parathyroid hormone (1-34) compensates the negative effect of smoking around implants, Clin Oral Implants Res 24 (9) (2013) 1055–1059.
[165] Y Ohkawa, K Tokunaga, N Endo, Intermittent administration of human parathyroid hormone (1-34) increases new bone formation on the interface of hydroxyapatitecoated titanium rods implanted into ovariectomized rat femora, J Orthop Sci 13 (6) (2008) 533–542.
[166] R Skripitz, P Aspenberg, Parathyroid hormone (1-34) increases attachment of PMMA cement to bone, J Orthop Sci 6 (6) (2001) 540–544.
[167] P Aspenberg, K Wermelin, P Tengwall, A Fahlgren, Additive effects of PTH and bisphosphonates on the bone healing response to metaphyseal implants in rats, Acta orthopaedica 79 (1) (2008) 111–115.
[168] T Rybaczek, S Tangl, T Dobsak, R Gruber, U Kuchler, The Effect of Parathyroid Hormone on Osseointegration in Insulin-Treated Diabetic Rats, Implant Dent 24 (4) (2015) 392–396.
[169] RA dos Santos, MS Ferreira, CE Mafra, M Holzhausen, LA de Lima, C Mendes Pannuti, JB César Neto, Synthetic parathyroid hormone may augment bone volume in autogenous grafts: a study in rats, J Periodontol 87 (1) (2016) 66–73.
[170] U Kuchler, T Spilka, K Baron, S Tangl, G Watzek, R Gruber, Intermittent parathyroid hormone fails to stimulate osseointegration in diabetic rats, Clin Oral Implants Res 22 (5) (2011) 518–523.
[171] YY Wu, T Yu, XY Yang, F Li, L Ma, Y Yang, XG Liu, YY Wang, P Gong, Vitamin D3 and insulin combined treatment promotes titanium implant osseointegration in diabetes mellitus rats, Bone 52 (1) (2013) 1–8.
[172] G Dvorak, A Fugl, G Watzek, S Tangl, P Pokorny, R Gruber, Impact of dietary vitamin D on osseointegration in the ovariectomized rat, Clin Oral Implants Res 23 (11) (2012) 1308–1313.
[173] Y Xiong, Y Zhang, Y Guo, Y Yuan, Q Guo, P Gong, Y Wu, 1alpha,25-Dihydroxyvitamin D3 increases implant osseointegration in diabetic mice partly through FoxO1 inactivation in osteoblasts, Biochem Biophys Res Commun 494 (3-4) (2017) 626–633.
[174] C Zhou, Y Li, X Wang, X Shui, J Hu, 1,25Dihydroxy vitamin D(3) improves titanium implant osseointegration in osteoporotic rats, Oral Surg Oral Med Oral Pathol Oral Radiol 114 (5 Suppl) (2012) S174–S178.
[175] J Kelly, A Lin, CJ Wang, S Park, I Nishimura, Vitamin D and bone physiology: demonstration of vitamin D deficiency in an implant osseointegration rat model, J Prosthodont 18 (6) (2009) 473–478.
[176] AS Virdi, J Irish, K Sena, M Liu, HZ Ke, MA McNulty, DR Sumner, Sclerostin antibody treatment improves implant fixation in a model of severe osteoporosis, J Bone Joint Surg Am 97 (2) (2015) 133–140.
[177] AS Virdi, M Liu, K Sena, J Maletich, M McNulty, HZ Ke, DR Sumner, Sclerostin antibody increases bone volume and enhances implant fixation in a rat model, J Bone Joint Surg Am 94 (18) (2012) 1670–1680.
[178] P Aspenberg, F Agholme, P Magnusson, A Fahlgren, Targeting RANKL for reduction of bone loss around unstable implants: OPG-Fc compared to alendronate in a model for mechanically induced loosening, Bone 48 (2) (2011) 225–230.
[179] Y Li, G Feng, Y Gao, E Luo, X Liu, J Hu, Strontium ranelate treatment enhances hydroxyapatite-coated titanium screws fixation in osteoporotic rats, J Orthop Res 28 (5) (2010) 578–582.
[180] L Maimoun, TC Brennan, I Badoud, V Dubois-Ferriere, R Rizzoli, P Ammann, Strontium ranelate improves implant osseointegration, Bone 46 (5) (2010) 1436–1441.
[181] Y Li, X Li, G Song, K Chen, G Yin, J Hu, Effects of strontium ranelate on osseointegration of titanium implant in osteoporotic rats, Clin Oral Implants Res 23 (9) (2012) 1038–1044.
[182] B Winnett, HC Tenenbaum, B Ganss, A Jokstad, Perioperative use of non-steroidal anti-inflammatory drugs might impair dental implant osseointegration, Clin Oral Implants Res 27 (2) (2016) e1–e7.
[183] RA Urdaneta, S Daher, J Lery, K Emanuel, SK Chuang, Factors associated with crestal bone gain on single-tooth locking-taper implants: the effect of nonsteroidal anti-inflammatory drugs, Int J Oral Maxillofac Implants 26 (5) (2011) 1063–1078.
[184] FV Ribeiro, FH Nociti Jr., EA Sallum, MZ Casati, Effect of aluminum oxide-blasted implant surface on the bone healing around implants in rats submitted to continuous administration of selective cyclooxygenase-2 inhibitors, Int J Oral Maxillofac Implants 24 (2) (2009) 226–233.
[185] FV Ribeiro, JB César-Neto, FH Nociti Jr, EA Sallum, AW Sallum, S De Toledo, MZ Casati, Selective cyclooxygenase-2 inhibitor may impair bone healing around titanium implants in rats, J Periodontol 77 (10) (2006) 1731–1735.
[186] AB Pablos, SA Ramalho, B Konig Jr., C Furuse, VC de Araujo, PR Cury, Effect of meloxicam and diclofenac sodium on peri-implant bone healing in rats, J Periodontol 79 (2) (2008) 300–306.
[187] SA Jacobsson, K Djerf, I Ivarsson, O Wahlstrom, Effect of diclofenac on fixation of hydroxyapatite-coated implants, An experimental study. J Bone Joint Surg Br. 76 (5) (1994) 831–833.
[188] WX Cai, L Ma, LW Zheng, A Kruse-Gujer, S Stübinger, NP Lang, RA Zwahlen, Influence of non-steroidal anti-inflammatory drugs (NSAIDs) on osseointegration of dental implants in rabbit calvaria, Clin Oral Implants Res 26 (4) (2015) 478–483.
[189] A Salduz, F Dikici, Kılıçoğlu ÖI, HI Balcı, T Akgul, M Kürkçü, C Kurtoğlu, R Tözün, Effects of NSAIDs and hydroxyapatite coating on osseointegration, J Orthop Surg (Hong Kong) 25 (1) (2017) 2309499016684410.
[190] T Trancik, W Mills, N Vinson, The effect of indomethacin, aspirin, and ibuprofen on bone ingrowth into a porous-coated implant, Clin Orthop Relat Res 249 (1989) 113–121.
[191] R Alissa, S Sakka, R Oliver, K Horner, M Esposito, HV Worthington, P Coulthard, Influence of ibuprofen on bone healing around dental implants: a randomised double-blind placebo-controlled clinical study, Eur J Oral Implantol 2 (3) (2009) 185–199.
[192] PE Persson, OS Nilsson, AM Berggren, Do non-steroidal anti-inflammatory drugs cause endoprosthetic loosening? A 10-year follow-up of a randomized trial on ibuprofen for prevention of heterotopic ossification after hip arthroplasty, Acta orthopaedica 76 (6) (2005) 735–740.
[193] S Sakka, SI. Hanouneh, Investigation of the effect of ibuprofen on the healing of osseointegrated oral implants, J Investig Clin Dent 4 (2) (2013) 113–119.
[194] DR Lionberger, PC. Noble, Celecoxib does not affect osteointegration of cementless total hip stems, J Arthroplasty 20 (7 Suppl 3) (2005) 115–122.
[195] A Meunier, P Aspenberg, L Good, Celecoxib does not appear to affect prosthesis fixation in total knee replacement: A randomized study using radiostereometry in 50 patients, Acta orthopaedica 80 (1) (2009) 46–50.
[196] X Zhang, SG Morham, R Langenbach, DA Young, L Xing, BF Boyce, EJ Puzas, RN Rosier, RJ O'Keefe, EM Schwarz, Evidence for a direct role of cyclo-oxygenase 2 in implant wear debris-induced osteolysis, J Bone Miner Res 16 (4) (2001) 660–670.
[197] JC Keller, TM Trancik, FA Young, E St Mary, Effects of indomethacin on bone ingrowth, J Orthop Res 7 (1) (1989) 28–34.
[198] L Sennerby, P Kalebo, P Thomsen, T Albrektsson, Influence of indomethacin on the regeneration of cortical bone within titanium implants in rabbits, Biomaterials 14 (2) (1993) 156–158.
[199] SD Cook, RL Barrack, JE Dalton, KA Thomas, TD Brown, Effects of indomethacin on biologic fixation of porous-coated titanium implants, J Arthroplasty 10 (3) (1995) 351–358.
[200] S Goodman, T Ma, M Trindade, T Ikenoue, I Matsuura, N Wong, N Fox, M Genovese, D Regula, RL Smith, COX-2 selective NSAID decreases bone ingrowth in vivo, J Orthop Res 20 (6) (2002) 1164–1169.
[201] MK Jeffcoat, MS Reddy, IC Wang, LA Meuninghoff, JB Farmer, DL Koth, The effect of systemic flurbiprofen on bone supporting dental implants, J Am Dent Assoc 126 (3) (1995) 305–311.
[202] K Hayashi, A Fotovati, S Abu Ali, Y Nakamura, M Inagaki, M Naito, Effect of a prostaglandin EP4 receptor agonist on early fixation of hydroxyapatite/titanium composite- and titanium-coated rough-surfaced implants in ovariectomized rats, J Biomed Mater Res A 92 (3) (2010) 1202–1209.
[203] R Nogueira-Filho Gda, T Cadide, BT Rosa, TG Neiva, R Tunes, D Peruzzo, Nociti FH Jr, JB César-Neto, Cannabis sativa smoke inhalation decreases bone filling around titanium implants: a histomorphometric study in rats, Implant Dent 17 (4) (2008) 461–470.
[204] M Duka, Z Lazic, N Stamatovic, Z Tatic, M Bubalo, M Veljovic, Clinical parameters of the local anesthetic effects of bupivacaine applied with and without a vasoconstrictor in oral implantology, Vojnosanit Pregl 64 (9) (2007) 611–615.
[205] LP Palin, TOB Polo, FRS Batista, PHS Gomes-Ferreira, IR Garcia Junior, AC Rossi, A Freire, LP Faverani, DH Sumida, R Okamoto, Daily melatonin administration improves osseointegration in pinealectomized rats, J Appl Oral Sci: revista FOB 26 (2018) e20170470.
[206] Y Jin, L Xu, X Hu, S Liao, JL Pathak, J Liu, Lithium chloride enhances bone regeneration and implant osseointegration in osteoporotic conditions, J Bone Miner Metab 35 (5) (2017) 497–503.
[207] X Wu, K Al-Abedalla, E Rastikerdar, S Abi Nader, NG Daniel, B Nicolau, F Tamimi, Selective serotonin reuptake inhibitors and the risk of osseointegrated implant failure: a cohort study, J Dent Res 93 (11) (2014) 1054–1061.
[208] BR Chrcanovic, J Kisch, T Albrektsson, A Wennerberg, Is the intake of selective serotonin reuptake inhibitors associated with an increased risk of dental implant failure? International J Oral Maxillofac Surg 46 (6) (2017) 782–788.
[209] D Balatsouka, K Gotfredsen, CH Lindh, T Berglundh, The impact of nicotine on bone healing and osseointegration, Clin Oral Implants Res 16 (3) (2005) 268–276.
[210] MSS Linden, ME Bittencourt, JP Carli, DC Miyagaki, PLD Santos, LR Paranhos, FC Groppo, JC Ramacciato, The effects of subcutaneous injection of nicotine on osseointegration of machined and anodized implants in rabbits, Acta cirurgica brasileira 33 (1) (2018) 31–39.
[211] J Berley, S Yamano, C Sukotjo, The effect of systemic nicotine on osseointegration of titanium implants in the rat femur, J Oral Implantol 36 (3) (2010) 185–193.
[212] S Yamano, JA Berley, WP Kuo, GO Gallucci, HP Weber, C Sukotjo, Effects of nicotine on gene expression and osseointegration in rats, Clin Oral Implants Res 21 (12) (2010) 1353–1359.

[213] JB Cesar-Neto, PM Duarte, EA Sallum, D Barbieri, H Moreno Jr., FH Nociti Jr., A comparative study on the effect of nicotine administration and cigarette smoke inhalation on bone healing around titanium implants, J Periodontol 74 (10) (2003) 1454–1459.
[214] EV Soares, WJ Favaro, VH Cagnon, CA Bertran, JA Camilli, Effects of alcohol and nicotine on the mechanical resistance of bone and bone neoformation around hydroxyapatite implants, J Bone Miner Metab 28 (1) (2010) 101–107.
[215] D Balatsouka, K Gotfredsen, CH Lindh, T Berglundh, The impact of nicotine on osseointegration, An experimental study in the femur and tibia of rabbits. Clin Oral Implants Res. 16 (4) (2005) 389–395.
[216] CM Stefani, F Nogueira, EA Sallum, TS de, AW Sallum, FH Nociti Jr., Influence of nicotine administration on different implant surfaces: a histometric study in rabbits, J Periodontol 73 (2) (2002) 206–212.
[217] K Gotfredsen, CH Lindh, T Berglundh, Does longstanding nicotine exposure impair bone healing and osseointegration? An experimental study in rabbits, J Biomed Mater Res B Appl Biomater 91 (2) (2009) 918–923.
[218] KF Bombonato-Prado, LG Brentegani, JA Thomazini, JJ Lachat, TL Carvalho, Alcohol intake and osseointegration around implants: a histometric and scanning electron microscopy study, Implant Dent 13 (3) (2004) 238–244.
[219] CP de Deco, AM da Silva Marchini, MA Barbara, LM de Vasconcellos, RF da Rocha, L Marchini, Negative effects of alcohol intake and estrogen deficiency combination on osseointegration in a rat model, J Oral Implantol 37 (6) (2011) 633–639.
[220] S Koo, B Konig Jr., CI Mizusaki, S Allegrini Jr., M Yoshimoto, MJ Carbonari, Effects of alcohol consumption on osseointegration of titanium implants in rabbits, Implant Dent 13 (3) (2004) 232–237.
[221] CC Lima, TD Silva, L Santos, WR Nakagaki, YC Loyola, MC Resck, JA Camilli, EA Soares, JA Garcia, Effects of ethanol on the osteogenesis around porous hydroxyapatite implants, Braz J Biol 71 (1) (2011) 115–119.
[222] L Minsk, AM. Polson, Dental implant outcomes in postmenopausal women undergoing hormone replacement, Compend Contin Educ Dent 19 (9) (1998) 859–862 64; quiz 66.
[223] M August, K Chung, Y Chang, J Glowacki, Influence of estrogen status on endosseous implant osseointegration, J Oral Maxillofac Surg 59 (11) (2001) 1285–1289 discussion 90-1.
[224] FH Nociti Jr., AW Sallum, EA Sallum, PM Duarte, Effect of estrogen replacement and calcitonin therapies on bone around titanium implants placed in ovariectomized rats: a histometric study, Int J Oral Maxillofac Implants 17 (6) (2002) 786–792.
[225] PM Duarte, JB Cesar-Neto, AW Sallum, EA Sallum, FH Nociti Jr., Effect of estrogen and calcitonin therapies on bone density in a lateral area adjacent to implants placed in the tibiae of ovariectomized rats, J Periodontol 74 (11) (2003) 1618–1624.
[226] PM Duarte, BC de Vasconcelos Gurgel, AW Sallum, GR Filho, EA Sallum, FH Nociti Jr., Alendronate therapy may be effective in the prevention of bone loss around titanium implants inserted in estrogen-deficient rats, J Periodontol 76 (1) (2005) 107–114.
[227] MC Qi, XQ Zhou, J Hu, ZJ Du, JH Yang, M Liu, XM Li, Oestrogen replacement therapy promotes bone healing around dental implants in osteoporotic rats, International J Oral Maxillofac Surg 33 (3) (2004) 279–285.
[228] Y Li, Y Gao, G Song, X Liu, J Hu, Additive effects of estrogen replacement therapy and bisphosphonates on osseointegration of hydroxyapatite-coated titanium screws in ovariectomized rats, Oral Surg Oral Med Oral Pathol Oral Radiol Endod 109 (5) (2010) 700–705.
[229] G Giro, CE Sakakura, D Goncalves, RM Pereira, E Marcantonio Jr., SR Orrico, Effect of 17beta-estradiol and alendronate on the removal torque of osseointegrated titanium implants in ovariectomized rats, J Periodontol 78 (7) (2007) 1316–1321.
[230] LY Shih, HN Shih, TH Chen, The effects of sex and estrogen therapy on bone ingrowth into porous coated implant, J Orthop Res 21 (6) (2003) 1033–1040.
[231] UM Maus, M Lühmann, JA Ohnsorge, S Andereya, H Schmidt, G Zombory, C Siebert, C Niedhart, [Dihydrotestosterone improves the osseointegration of cobalt-chromium implants], Z Orthop Unfall 151 (1) (2013) 25–30.
[232] P Peichl, R Marteau, A Griesmacher, W Kumpan, R Schedl, E Prosquil, P Fasol, H Bröll, Calcitonin nasal spray treatment for postmenopausal women after hip fracture with total hip arthroplasty, J Bone Miner Metab 23 (3) (2005) 243–252.
[233] IO Arnala, Salmon calcitonin (Miacalcic ns 200 IU) in prevention of bone loss after hip replacement, Scand J Surg 101 (4) (2012) 249–254.
[234] FH Nociti Jr., EA Sallum, S Toledo, HN Newman, AW Sallum, Effect of calcitonin on bone healing following titanium implant insertion, J Oral Sci 41 (2) (1999) 77–80.
[235] S Feitosa Dda, B Bezerra Bde, GM Ambrosano, FH Nociti, MZ Casati, EA Sallum, S de Toledo, Thyroid hormones may influence cortical bone healing around titanium implants: a histometric study in rats, J Periodontol 79 (5) (2008) 881–887.
[236] M Wang, L Lan, T Li, J Li, Y Li, The effect of oxytocin on osseointegration of titanium implant in ovariectomized rats, Connect Tissue Res 57 (3) (2016) 220–225.
[237] W Maiquan, P Liwei, L Yunfeng, [Efficacy of systemic administration of oxytocin on implant osseointegration in osteoporotic rats], Hua Xi Kou Qiang Yi Xue Za Zhi 34 (4) (2016) 332–335.
[238] T Fujimoto, A Niimi, T Sawai, M Ueda, Effects of steroid-induced osteoporosis on osseointegration of titanium implants, Int J Oral Maxillofac Implants 13 (2) (1998) 183–189.
[239] V Petsinis, G Kamperos, F Alexandridi, K Alexandridis, The impact of glucocorticosteroids administered for systemic diseases on the osseointegration and survival of dental implants placed without bone grafting-A retrospective study in 31 patients, J Craniomaxillofac Surg 45 (8) (2017) 1197–1200.
[240] RS Avedian, RE Goldsby, MJ Kramer, RJ O'Donnell, Effect of chemotherapy on initial compressive osseointegration of tumor endoprostheses, Clin Orthop Relat Res 459 (2007) 48–53.
[241] AF. Kovacs, Influence of chemotherapy on endosteal implant survival and success in oral cancer patients, International J Oral Maxillofac Surg 30 (2) (2001) 144–147.
[242] DR Young, LY Shih, MG Rock, FJ Frassica, P Virolainen, EY Chao, Effect of cisplatin chemotherapy on extracortical tissue formation in canine diaphyseal segmental replacement, J Orthop Res 15 (5) (1997) 773–780.
[243] H Al-Mahalawy, HF Marei, H Abuohashish, H Alhawaj, M Alrefaee, B Al-Jandan, Effects of cisplatin chemotherapy on the osseointegration of titanium implants, J Craniomaxillofac Surg 44 (4) (2016) 337–346.
[244] P Virolainen, N Inoue, M Nagao, FJ Frassica, EY Chao, The effect of multidrug chemotherapy on bone graft augmented prosthesis fixation, J Orthop Res 23 (4) (2005) 795–801.
[245] JB Carvas, RM Pereira, E Bonfá, CA Silveira, LL Lima, F Caparbo Vde, SB Mello, No deleterious effect of low dose methotrexate on titanium implant osseointegration in a rabbit model, Clinics (Sao Paulo) 66 (6) (2011) 1055–1059.
[246] B Mair, G Fuerst, P Kubitzky, S Tangl, H Bergmeister, U Losert, G Watzek, R Gruber, The anti-angiogenic substance TNP-470 impairs peri-implant bone formation: a pilot study in the rabbit metaphysis model, Clin Oral Implants Res 18 (3) (2007) 370–375.
[247] AE Al Subaie, H Eimar, MN Abdallah, R Durand, J Feine, F Tamimi, E Emami, Anti-VEGFs hinder bone healing and implant osseointegration in rat tibiae, J Clin Periodontol 42 (7) (2015) 688–696.
[248] KE. El-Kholey, Efficacy of two antibiotic regimens in the reduction of early dental implant failure: a pilot study, Int J Oral Maxillofac Surg 43 (4) (2014) 487–490.
[249] M Esposito, G Cannizzaro, P Bozzoli, L Checchi, V Ferri, S Landriani, M Leone, M Todisco, C Torchio, T Testori, F Galli, P Felice, Effectiveness of prophylactic antibiotics at placement of dental implants: a pragmatic multicentre placebo-controlled randomised clinical trial, Eur J Oral Implantol 3 (2) (2010) 135–143.
[250] A Caiazzo, P Casavecchia, A Barone, F Brugnami, A pilot study to determine the effectiveness of different amoxicillin regimens in implant surgery, J Oral Implantol 37 (6) (2011) 691–696.
[251] H Kashsni, C Dahlin, B Alse'n, Influence of different prophylactic antibiotic regimens on implant survival rate: a retrospective clinical study, Clin Implant Dent Relat Res 7 (1) (2005) 32–35.
[252] G Giro, J In, L Witek, R Granato, C Marin, PG Coelho, JC Ramacciato, RH Motta, Amoxicillin administrations and its influence on bone repair around osseointegrated implants, J Oral Maxillofac Surg 72 (2) (2014) 305 e1-e5.
[253] JA Kopman, DM Kim, SS Rahman, JA Arandia, NY Karimbux, JP Fiorellini, Modulating the effects of diabetes on osseointegration with aminoguanidine and doxycycline, J Periodontol 76 (4) (2005) 614–620.
[254] JP Fiorellini, ML Nevins, A Norkin, HP Weber, NY Karimbux, The effect of insulin therapy on osseointegration in a diabetic rat model, Clin Oral Implants Res 10 (5) (1999) 362–368.
[255] JT Siqueira, SC Cavalher-Machado, VE Arana-Chavez, P Sannomiya, Bone formation around titanium implants in the rat tibia: role of insulin, Implant Dent 12 (3) (2003) 242–251.
[256] MS McCracken, R Aponte-Wesson, R Chavali, JE Lemons, Bone associated with implants in diabetic and insulin-treated rats, Clin Oral Implants Res 17 (5) (2006) 495–500.
[257] RS de Molon, JA Morais-Camilo, MH Verzola, RS Faeda, MT Pepato, E Marcantonio Jr., Impact of diabetes mellitus and metabolic control on bone healing around osseointegrated implants: removal torque and histomorphometric analysis in rats, Clin Oral Implants Res 24 (7) (2013) 831–837.
[258] PT Kwon, SS Rahman, DM Kim, JA Kopman, NY Karimbux, JP Fiorellini, Maintenance of osseointegration utilizing insulin therapy in a diabetic rat model, J Periodontol 76 (4) (2005) 621–626.
[259] JA de Morais, IK Trindade-Suedam, MT Pepato, E Marcantonio Jr., A Wenzel, G Scaf, Effect of diabetes mellitus and insulin therapy on bone density around osseointegrated dental implants: a digital subtraction radiography study in rats, Clin Oral Implants Res 20 (8) (2009) 796–801.
[260] R Margonar, CE Sakakura, M Holzhausen, MT Pepato, Alba jR, Marcantonio jE, The influence of diabetes mellitus and insulin therapy on biomechanical retention around dental implants: a study in rabbits, Implant Dent 12 (4) (2003) 333–339.
[261] CR Serrao, MF Bastos, DF Cruz, F de Souza Malta, PC Vallim, PM Duarte, Role of Metformin in Reversing the Negative Impact of Hyperglycemia on Bone Healing Around Implants Inserted in Type 2 Diabetic Rats, Int J Oral Maxillofac Implants 32 (3) (2017) 547–554.
[262] KA Inouye, FC Bisch, ME Elsalanty, I Zakhary, RM Khashaba, JL Borke, Effect of metformin on periimplant wound healing in a rat model of type 2 diabetes, Implant Dent 23 (3) (2014) 319–327.
[263] RP Guimaraes, PA de Oliveira, AM Oliveira, Effects of induced diabetes and the administration of aminoguanidine in the biomechanical retention of implants: a study in rats, J Periodontal Res 46 (6) (2011) 691–696.
[264] X Wu, K Al-Abedalla, H Eimar, S Arekunnath Madathil, S Abi-Nader, NG Daniel, B Nicolau, F Tamimi, Antihypertensive Medications and the Survival Rate of Osseointegrated Dental Implants: A Cohort Study, Clin Implant Dent Relat Res 18 (6) (2016) 1171–1182.

[265] AE Al-Subaie, M Laurenti, MN Abdallah, I Tamimi, F Yaghoubi, H Eimar, N Makhoul, F Tamimi, Propranolol enhances bone healing and implant osseointegration in rats tibiae, J Clin Periodontol 43 (12) (2016) 1160–1170.
[266] PM Duarte, GR Nogueira Filho, EA Sallum, AW Sallum, FH Nociti Junior, Short--term immunosuppressive therapy does not affect the density of the pre-existing bone around titanium implants placed in rabbits, Pesqui Odontol Bras 17 (4) (2003) 362–366.
[267] A Lübbeke, G Garavaglia, KJ Rothman, A Bonvin, C Roussos, H Miozzari, P Hoffmeyer, Statins may reduce femoral osteolysis in patients with total Hip arthroplasty, J Orthop Res 31 (5) (2013) 814–820.
[268] Y Ayukawa, A Okamura, K Koyano, Simvastatin promotes osteogenesis around titanium implants, Clin Oral Implants Res 15 (3) (2004) 346–350.
[269] K Basarir, B Erdemli, A Can, E Erdemli, T Zeyrek, Osseointegration in arthroplasty: can simvastatin promote bone response to implants? Int Orthop 33 (3) (2009) 855–859.
[270] H Yin, J Li, X Yu, Z Fu, Effects of simvastatin on osseointegration in a canine total hip arthroplasty model: an experimental study, J Arthroplasty 26 (8) (2011) 1534–1539.
[271] Z Du, J Chen, F Yan, Y Xiao, Effects of Simvastatin on bone healing around titanium implants in osteoporotic rats, Clin Oral Implants Res 20 (2) (2009) 145–150.
[272] Z Du, J Chen, F Yan, N Doan, S Ivanovski, Y Xiao, Serum bone formation marker correlation with improved osseointegration in osteoporotic rats treated with simvastatin, Clin Oral Implants Res 24 (4) (2013) 422–427.
[273] Y Ayukawa, Y Ogino, Y Moriyama, I Atsuta, Y Jinno, M Kihara, Y Tsukiyama, K Koyano, Simvastatin enhances bone formation around titanium implants in rat tibiae, J Oral Rehabil 37 (2) (2010) 123–130.
[274] B Ma, SA Clarke, RA Brooks, N Rushton, The effect of simvastatin on bone formation and ceramic resorption in a peri-implant defect model, Acta biomaterialia 4 (1) (2008) 149–155.
[275] B Faensen, C Hain, J Höhne, P Schwabe, N Haas, G Schmidmaier, B Wildemann, Aprotinin application has no negative effect on osseous implant integration: a biomechanical and histomorphometric investigation in a rat model, Arch Orthop Trauma Surg 129 (1) (2009) 51–56.
[276] BC Callahan, EJ Lisecki, RE Banks, JE Dalton, SD Cook, JD Wolff, The effect of warfarin on the attachment of bone to hydroxyapatite-coated and uncoated porous implants, J Bone Joint Surg Am 77 (2) (1995) 225–230.
[277] CE Sakakura, R Margonar, R Sartori, JA Morais, E Marcantonio Jr., The influence of cyclosporin a on mechanical retention of dental implants previously integrated to the bone: a study in rabbits, J Periodontol 77 (12) (2006) 2059–2062.
[278] CE Sakakura, E Marcantonio Jr., A Wenzel, G Scaf, Influence of cyclosporin A on quality of bone around integrated dental implants: a radiographic study in rabbits, Clin Oral Implants Res 18 (1) (2007) 34–39.
[279] PM Duarte, GR Nogueira Filho, EA Sallum, S de Toledo, AW Sallum, FH Nociti Junior, The effect of an immunosuppressive therapy and its withdrawal on bone healing around titanium implants, A histometric study in rabbits. J Periodontol. 72 (10) (2001) 1391–1397.
[280] AA El Hadary, HH Yassin, ST Mekhemer, JC Holmes, M Grootveld, Evaluation of the effect of ozonated plant oils on the quality of osseointegration of dental implants under the influence of Cyclosporin A an in vivo study, J Oral Implantol 37 (2) (2011) 247–257.
[281] CE Sakakura, R Margonar, M Holzhausen, FH Nociti Jr., RC Alba Jr., E Marcantonio Jr., Influence of cyclosporin A therapy on bone healing around titanium implants: a histometric and biomechanic study in rabbits, J Periodontol 74 (7) (2003) 976–981.
[282] A Ekelund, P Aspenberg, O Nilsson, No effect of immunosuppression with cyclosporin A detected on bone ingrowth into cancellous allo- and xenografts in the rat, Acta Orthop Scand 70 (5) (1999) 491–496.
[283] X Zheng, A Mo, Y Wang, Y Guo, Y Wu, Q Yuan, Effect of FK-506 (tacrolimus) therapy on bone healing of titanium implants: a histometric and biomechanical study in mice, Eur J Oral Sci 125 (1) (2017) 28–33.
[284] X Wu, K Al-Abedalla, S Abi-Nader, NG Daniel, B Nicolau, F Tamimi, Proton Pump Inhibitors and the Risk of Osseointegrated Dental Implant Failure: A Cohort Study, Clin Implant Dent Relat Res 19 (2) (2017) 222–232.
[285] BR Chrcanovic, J Kisch, T Albrektsson, A Wennerberg, Intake of Proton Pump Inhibitors Is Associated with an Increased Risk of Dental Implant Failure, Int J Oral Maxillofac Implants 32 (5) (2017) 1097–1102.
[286] A Al Subaie, E Emami, I Tamimi, M Laurenti, H Eimar, MN Abdallah, F Tamimi, Systemic administration of omeprazole interferes with bone healing and implant osseointegration: an in vivo study on rat tibiae. Systemic administration of omeprazole interferes with bone healing and implant osseointegration: an in vivo study on rat tibiae, J Clin Periodontol. 43 (2) (2016) 193–203.
[287] HA Altug, U Tatli, AT Coskun, Erdogan Ö, A Özkan, M Sencimen, M Kürkçü, Effects of hyperbaric oxygen treatment on implant osseointegration in experimental diabetes mellitus, J Appl Oral Sci: revista FOB 26 (2018) e20180083.
[288] PA Oliveira, AM Oliveira, AB Pablos, FO Costa, GA Silva, JN Santos, PR Cury, Influence of hyperbaric oxygen therapy on peri-implant bone healing in rats with alloxan-induced diabetes, J Clin Periodontol 39 (9) (2012) 879–886.
[289] J Nyberg, S Hertzman, B Svensson, CB Johansson, Osseointegration of implants in irradiated bone with and without hyperbaric oxygen treatment: an experimental study in rat Tibiae, Int J Oral Maxillofac Implants 28 (3) (2013) 739–746.
[290] K Hayashi, A Fotovati, SA Ali, K Oda, H Oida, M Naito, Prostaglandin EP4 receptor agonist augments fixation of hydroxyapatite-coated implants in a rat model of osteoporosis, J Bone Joint Surg Br 87 (8) (2005) 1150–1156.
[291] T Aghaloo, J Pi-Anfruns, A Moshaverinia, D Sim, T Grogan, D Hadaya, The Effects of Systemic Diseases and Medications on Implant Osseointegration: A Systematic Review, Int J Oral Maxillofac Implants 34 (2019) s35–s49.
[292] F Frizzera, MHA Verzola, RS de Molon, GJPL de Olivieira, G Giro, LC Spolidorio, RMR Pereira, S Tetradis, JA Cirelli, SRP Orrico, Evaluation of bone turnover after bisphosphonate withdrawal and its influence on implant osseointegration: an in vivo study in rats, Clin Oral Investig 23 (4) (2019) 1733–1744.
[293] A Khojasteh, MM Dehghan, P Nazeman, Immediate implant placement following 1-year treatment with oral versus intravenous bisphosphonates: a histomorphometric canine study on peri-implant bone, Clin Oral Investig 23 (4) (2019) 1803–1809.
[294] HA Altug, U Tatli, AT Coskun, O Erdogan, A Ozkan, M Sencimen, M Kurkcu, Effects of hyperbaric oxygen treatment on implant osseointegration in experimental diabetes mellitus, J Appl Oral Sci 26 (2018) e20180083.
[295] CES Mafra, M Sirolli, MC Cavalcanti, RBAD Santos, CM Pannuti, GA Romito, JBC Neto, Effect of Different Doses of Synthetic Parathyroid Hormone (1-34) on Bone around Implants: a Preclinical Rat Model, Braz Dent J 30 (1) (2019) 43–46.
[296] B. Al-Jandan, Effect of antiangiogenic targeted chemotherapy on the osseointegration of titanium implants in rabbits, Br J Oral Maxillofac Surg 57 (2) (2019) 157–163.
[297] A Pandey, S Verma, S Malhan, N Mittal, A Chaudhary, T Gera, Evaluation of Effect of Bisphosphonates on Dental Implant Therapy in Postmenopausal Women Using Cone Beam Computed Tomography, J Contemp Dent Pract 20 (1) (2019) 51–55.
[298] P Korn, I Kramer, F Schlottig, N Todtman, U Eckelt, A Burki, SJ Ferguson, A Kautz, M Schnabelrauch, U Range, M Kneissel, B Stadlinger, Systemic sclerostin antibody treatment increases osseointegration and biomechanical competence of zoledronic-acid-coated dental implants in a rat osteoporosis model, Eur Cell Mater 37 (2019) 333–346.
[299] CRG Bautista, IVD Santos, RM Moraes, FY Chiba, DH Sumida, MB de Mraes, LMR de Vasconcellos, Anbinder. Sitagliptin's effects on bone tissue and osseointegration in diabetic rats, Arch Oral Biol 102 (2019) 238–243.
[300] MVM Dantas, MHA Verzola, PV Sanitá, LN Dovigo, PS Cerri, MAC Gabrielli, The influence of Cisplatin-based chemotherapy on the osseointegration of dental implants: An in vivo mechanical and histometrical study, Clin Oral Implants Res 30 (7) (2019) 603–616.
[301] M Hou, RSB Lee, Z Du, SM Hamlet, C Vaquette, S Ivanovski, The influence of high-dose systemic zoledronate administration on osseointegration of implants with different surface topography, J Periodontal Res 54 (6) (2019) 633–643.
[302] T Jia, YN Wang, J Zhang, X Hao, D Zhang, X Xu, Cinaciguat in combination with insulin induces a favorable effect on implant osseointegration in type 2 diabetic rats, Biomed Pharmacother 118 (2019) 109216.
[303] D Apostu, O Lucaciu, A Mester, D Oltean-Dan, D Gheban, HRC Benea, Tibolone, alendronate, and simvastatin enhance implant osseointegration in a preclinical in vivo model, Clin Oral Implants Res 31 (7) (2020) 655–668.
[304] L Abu Nada, A Al Subaie, A Mansour, X Wu, M-N Abdallah, H Al-Waeli, A Ersheidat, LS Stone, M Murshed, F Tamimi, The antidepressant drug, sertraline, hinders bone healing and osseointegration in rats' tibiae, J Clin Periodontol 45 (12) (2018) 1485–1497.
[305] R Skripitz, P. Aspenberg, Early effect of parathyroid hormone (1-34) on implant fixation, Clin Orthop and Relat Res 392 (2001) 427–432.