Osseointegration Pharmacology: A Systematic Mapping Using Artificial Intelligence

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Dedication

I would like to dedicate my thesis to my sweet and loving parents (mother and father) for their endless love and support throughout this thesis. It is also dedicated to my wife (Tahani) and my daughter (Naya), for all the wonderful things, loves and supports they bring to my life. It is also dedicated to my brothers (Ahmed, Ibrahim, Abdullah), sisters (Zainab, Amnah, Fatimah, Hana, Entissar, Hanan), my best friend Raoof Abbas

Abstract

Introduction

There is growing evidence associating patient systemic conditions and medications to the success of osseointegrated medical devices such as dental implants and hip prosthesis. However, bibliographic assessment of these associations cannot be fully achieved with conventional systematic reviews due to the broad scope of the question addressed. Evidence mapping methods are better suited to such a task; however, evidence mapping can be very resource-intensive.

Artificial intelligence can be used to reduce the workload associated with systematic reviews (SR) and systematic mappings (SM). However, the available methods are limited in their ability to reduce the workload and their sensitivity and specificity. A limiting factor is the quality of the training datasets used for machine learning.

Hypothesis

Systematic mapping of the effect of medications on bone-implant osseointegration can be successfully achieved using a machine learning (ML) algorithm trained with similar and non-similar training datasets.

Objective

The objective of this study was to develop a method for systematic mapping of the literature using a machine learning algorithm trained with similar and non-similar training datasets and use this to identify the effect of medications on bone-implant osseointegration.

Methods

To produce high-quality training datasets for machine learning, we conducted precise search strategies to produce similar and non-similar articles using PubMed. The articles were screened manually and classified into include and excluded articles. The inclusion criteria were clinical and animal studies that assessed the effect of systemic medication on bone-implant osseointegration.

The dataset of included and excluded articles screened manually were used to train a machine-learning algorithm based on Support Vector Machines (SVM). The algorithm produced was validated against a published systematic review with a search strategy that falls within the scope of ours. Then, the trained algorithm was used to screen articles identified with a highly sensitive search strategy (543927 articles).

Results

Our algorithm was able to screen half-million published articles and reduce the workload by 95% with an accuracy of 95%, a False Positive Rate (TFP) of 95%, a sensitivity of 93%, and a specificity of 95%. The number of articles retrieved and included for the final analysis was 268 articles. In these articles, we identified 31 drug families that have been studied for their effect on osseointegration.

Conclusion

Partial automation of systematic mappings can be successfully achieved with similar and non-similar training datasets classified by MeSH-terms. This method allowed us to perform a systematic mapping on the effect of medications on bone-implant osseointegration, and we identified 31 drugs that affect osseointegration.

Résumé

Introduction : Il existe un nombre croissant de publication associant les patients polymédiqués à un risque plus important de non ostéointégration des implants dentaires et des prothèses de hanche. Cependant, la littérature contient un nombre très important de publication sur le sujet, ce qui rend l'analyse systématiques très compliqué. Récemment, des méthodes de cartographie de la littérature (ou mapping review) ont été proposé pour réaliser ce genre de synthèse. Cependant, ce type de travail nécessite beaucoup de temps et de ressources. Ainsi, l'intelligence artificielle pourrait être utilisée pour réduire la charge de travail demandé lors de la réalisation de ce type de cartographies systématiques. Les méthodes disponibles sont actuellement limitées en termes de performance, notamment en termes de sensibilité et leur spécificité. Ces performances s'expliquent principalement par la qualité et le nombre de données utilisés pendant la phase d'apprentissage de l'algorithme.

Hypothèse : Nous pensons qu'il est possible de réaliser une cartographie systématique de l'effet des médicaments sur l'ostéointégration des implants osseux en utilisant un algorithme d'apprentissage automatique formé avec des données de formation similaires et non similaires.

Objectif : Lors de ce travail, nous souhaitons développer une méthode de cartographie systématique de la littérature à l'aide d'un algorithme d'apprentissage automatique formé à partir d'ensembles de données de formation similaires et non similaires, et de l'utiliser pour identifier l'effet des médicaments sur l'ostéointégration des implants en os.

Matériels et Méthodes : Afin de produire des articles similaires et non similaires, un protocole de recherche précis a été développé pour extraire des articles à partir de la base de données PubMed. Les articles ont d'abord été triés et classés manuellement pour rechercher les articles similaires et

non similaires. Les critères d'inclusion étaient des études cliniques et animales évaluant l'effet d'un médicament systémique sur l'ostéointégration des implants osseux. Les articles inclus et exclus ont été utilisés pour former un algorithme d'apprentissage automatique basé sur des machines à vecteurs de support. L'algorithme a été ensuite validé par comparaison avec une revue systématique préalablement publiée. Enfin, l'algorithme a été utilisé pour sélectionner les articles identifiés par une stratégie de recherche extrêmement sensible.

Résultats : L'algorithme a été capable d'analyser un demi-million d'articles publiés et de réduire la charge de travail de 93% avec une précision de 95%, un taux de faux positifs (TFP) de 95%, une sensibilité de 93% et une spécificité de 95%, en comparaison avec la revue systématique déjà publiée. Le nombre d'articles récupérés et inclus pour l'analyse finale était de 266 articles. Dans ces articles, nous avons identifié 31 familles de médicaments qui ont été étudiés pour leur effet sur l'ostéointégration.

Conclusion : Ce travail a permis de créer un algorithme capable d'identifier et de sélectionner avec succès un ensemble d'article à partir des termes MeSH , avec une précision très proche de celle réalisé par le travail préalablement. Cette méthode nous a permis de réaliser une cartographie systématique de l'effet 31 médicaments sur l'ostéointégration des implants osseux.

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Contribution of Authors

This thesis includes one manuscript entitled "**Osseointegration Pharmacology: A Systematic Mapping Using Artificial Intelligence**."

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Contribution: M.M. wrote the manuscript, performed data extraction and data screening, collected and analyzed the data and performed statistical analysis, helped in applying artificial intelligence (AI) for collecting data, and also for quality assessments. F.B. wrote the AI scripts, N.S. applied the AI for the collecting data and helped in data extraction, and R.R. and A.D. wrote the quality assessment and helped in data extraction. M.A. assisted in quality assessments. K.Y.W. collected data for the method. M.F. helped in data extraction. F.T. prepared and supervised the work, provided scientific guidance, and reviewed the manuscript. D.T. and M.D. reviewed the manuscript.

Originality: This is the first study to use a semi-automated evidence mapping review to synthesize the effect of drugs on bone-implant osseointegration. The results of this study revealed that drugs known to affect the metabolic activities involved in the process of osseointegration could affect osseointegration.

Chapter 1: Introduction and Research Rationale

1.1 Thesis outline

This thesis consists of three chapters. The first chapter includes the thesis outline, the research rationale, the hypothesis, and the objectives. The second chapter includes the literature review introducing bone composition and physiology as well as the concepts of osseointegration, systematic reviews, and systematic mapping reviews. And the third chapter includes one manuscript entitled "**Osseointegration Pharmacology: A Systematic Mapping Using Artificial Intelligence**."

1.2 Research rationale, hypothesis, and objectives

Osseointegration plays an essential role in the success of many bone-anchored medical devices such as orthopedic prosthesis, auditory devices, and dental implants (1, 2). Bone healing and metabolism play a crucial role in the process of osseointegration and in determining the success or failure of bone-anchored implants. Failure of osseointegration can lead to serious deleterious outcomes with orthopedics, auditory, and dental implants such as impairments of function and aesthetic, infections, pain, bone loss, and implant failure (1, 2). Some systemic drugs have been found to influence bone metabolism and affect bone-implant osseointegration (3). This raises the question of how relevant are the possible side effects of medications on osseointegration. Addressing this question could help us better understand the biological mechanisms of osseointegration and improve clinical decision making (4). However, complex open questions such as "what drugs affect osseointegration?" are too extensive for a conventional systematic review to address. Evidence mapping reviews were developed to address this type of question and help clinicians, patients, and researchers make better evidence-based decisions (4). However, the size of the healthcare scientific literature is enormous; thus, full systemic mapping and subject-wide

evidence synthesis are usually not feasible. So, very recently, Machine Learning has been introduce for fully or semi-automated evidence mapping reviews and this approach has achieved very promising results (5, 6).

Accordingly, we hypothesize that systematic mapping of the effect of medications on bone-implant osseointegration can be successfully achieved using machine learning (ML).

The specific objective of this thesis:

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?". More specifically, this thesis aimed to identify the list of drugs known to impair and enhance osseointegration. To achieve this, we developed a method to generate a ML classifier for automated article screening for systematic mappings.

Chapter 2: Literature Review

2.1 Bone

Bone is a mineralized dense, supportive connective tissue. It is essential for protecting vital organs, storing minerals, producing hematopoietic cells, and enabling locomotion (7). It plays an important biological role in regulating mineral homeostasis and energy metabolism. Also, bone cooperates with other vital tissues and organs such as the hypothalamus, the adipose tissue, the kidney, the vasculature, and the parathyroid gland, among others, in order to carry out metabolic processes that keep the human body in balance (7).

The structure of bone consists of the periosteum, the compact bone, the spongy bone, and the medullary cavity (8, 9). The periosteum is the outer layer that covers the bone surface, and it consists of dense irregular connective tissue, nerve fibers, blood, and lymph vessels (9). The compact bone consists of a very dense lamellar bone without trabeculae that contain several canals to provide access for nerves, blood vessels, and lymphatic ducts (9). The spongy bone consists of trabeculae made of irregularly arranged lamellae and osteocytes interconnected by canaliculi that work as struts (9). The medullary cavity is the innermost part of the bone, and it is an open cavity filled with red and/or yellow bone marrow. This area is involved in the formation of hematopoietic cells and other specialized cells, such as mesenchymal stem cells and osteoprogenitor cells (8, 9).

2.1.1 Bone Cells

There are three main types of bone cells:

A. Osteoblasts are mature bone cells responsible for synthesizing new bone. Osteoblasts produce osteoid, an extracellular matrix of collagen and non-collagenous proteins as well as proteoglycans, glycoproteins that are eventually calcified (10). Osteoblasts rely on a variety of

transmembranous proteins (e.g., integrins, connexins, cadherins cytokines), hormones, and growth factors that maintain their cellular function and responsiveness to metabolic and mechanical stimuli. They are located at the bone surface forming a tight layer of single nucleus cells (11). Human osteoblasts live up to 8 weeks until some of these cells get trapped in their calcified matrix and then develope into osteocytes (11).

B. Osteocytes are mature cells that maintain the bone matrix. They are derived from osteoblast but have a different morphology and function. In terms of morphology, the nucleolus-to-cytoplasm ratio of osteocytes is large compared to osteoblasts. Also, osteocytes have fewer ribosomes and smaller endoplasmic reticula (11). Osteocytes have a large number of cytoplasmic extensions that keep them connected to each other and with bone-lining cells (11).

C. Osteoclasts are multinucleated, giant, highly migratory, and polarized cells that secrete acids and protein-digesting enzymes. Their main function is osteolysis, which is the dissolution of the bone matrix and release of stored minerals. Often, they are found lining in the endosteum and bone marrow (11).

2.1.2 Bone Development

Bone formation relies mainly on two distinct processes, endochondral ossification and intramembranous ossification (12) (9). Endochondral ossification is the process of bone formation that occurs by replacing hyaline cartilage structures with calcified bone, and it is responsible for the formation of the long bone. Intramembranous ossification is the process of bone formation that occurs by mesenchymal tissue, and then these mesenchymal stem cells differentiate into osteoblasts, which secrete osteoid that later on calcifies to form bone, such as skull, maxilla, and clavicles formation (9).

2.1.3 Bone remodeling

Bone remodeling is the process that involves an ongoing cycle of bone resorption and formation, which is essential for maintaining bone mechanical strength. Bone remodeling is modulated by two types of cells: osteoclasts that resorb bone (breaking down the old bone) and osteoblasts that are responsible for synthesizing new bone (11, 13). Bone remodeling should be tightly regulated; otherwise, imbalanced bone resorption and bone formation may lead to medical condition with either excess bone loss such as osteoporosis or excess bone formation such as osteopetrosis (13).

2.1.4 Bone Healing

Bone healing is a physiological process that aims to repair bone fracture (14). There are two histological types of bone healing: primary and secondary bone healing (14). Primary healing is rare and needs high stability and absolute contact of the bone fragments in order to directly re-establish an anatomically and biomechanically competent lamellar bone structure (14, 15). Secondary bone healing, the most common healing process, occurs in the vast majority of bone injuries, and it consists of two mechanisms intramembranous and endochondral ossification (14, 15).

Bone healing involves four distinct but overlapping stages: Haemostasis, Inflammation, Proliferation, and Remodeling (16), details underneath:

A- Haemostasis stage: This stage begins upon trauma immediately after bleeding, and its duration takes from minutes to hours. During this stage, a series of biological processes occur, such as coagulation and platelet activation. Also, proteins, as well as growth and differentiation factors (e.g., heparin-binding domains by heparin hydrolases from blood platelets) that are stored in the bone matrix, become soluble and active (17, 18).

B- Inflammatory stage: This stage starts minutes after bone injury and lasts for a few days (18). During this stage, a series of biological processes occur, such as cytokine release, and the onset of the macrophage-mediated inflammation, resulting in the formation of granulation tissue (16).

C- Proliferative stage: This stage begins three days after injury, and it can continue for up to 5-6 weeks. This stage is characterized by neovascularization and cell differentiation at the injury site, followed by cell proliferation and activation. Fibroblasts begin to produce an immature connective tissue matrix to support vascular ingrowth (16, 19). Subsequently, osteoblasts arrive at the site and start secreting a collagen matrix and osteoid in order to form immature woven bone (16, 19).

D- Remodeling (maturation) stage: This is the last stage of bone healing, and it takes place over months to years in order to restore the bone into its original shape, structure, and mechanical strength (16, 19). Remodeling of the immature bone matrix involves resorption and deposition of bone in response to mechanical stress (19).

2.2 Osseointegration

The term osseointegration derives from the Greek word ‘osteon,’ which means bone, and the Latin word‘integrate,’ which means ‘to make whole’ (20). The first definition of osseointegration was provided by Professor Branemark as an intimate contact between the surface of an implant and bone without interposed soft tissue layers (20). These implants are mainly made of titanium due to its excellent biocompatibility, good resistance to corrosion, and lack of toxicity, and ability to create a firm and lasting connection with the recipient bone (1, 2). On the other hand, the biological events involved in the process of osseointegration resemble those of bone fracture healing at least during the initial host response, which includes hematoma formation and direct migration of mesenchymal cells through the clot matrix to the implant surface in order to initiate woven bone

formation through the intramembranous pathway, and lamellar bone formation on the spicules of woven bone (21).

These biological events and implant success depend on implant stability. There are two main types of implant stability, the primary and secondary stability: Primary implant stability is defined as the mechanical interlocking of the implant in the bone bed without any mobility. It depends mainly on the bone's quality and quantity, and it is highly associated with successful implant integration and long-term clinical outcome (22). Adequate osteotomy preparation is key for high bone-to-implant contact (BIC), mechanical primary implant stability, and healing (23). Secondary implant stability is defined as the stability that comes through the process of osseointegration. This type of stability occurs at the process of regeneration and remodeling happing at the bone-implant interface (24), and it relies on both metabolic activities and the nature of the implant surface. Failure of osseointegration between the implant and bone can occur: during the early stages of osseointegration due to lack of intimate bone-implant contact or at later stages due to the disruption of the established contact by biological conditions such as infection or mechanical overload and fracture (2, 25). Failure of osseointegration devices could have serious consequences on patients' life, in terms of increased morbidity and mortality (e.g., hip replacement) as well as socio-economical costs due to re-intervention procedures (26).

2.3 Systematic reviews (SR)

Access to the ever-growing medical scientific information is time-consuming and overwhelming. This problem could be addressed through systematic reviews, a type of scientific publication designed to answer very specific questions (e.g., does aspirin increase the risk of implant failure in a specific population?) by performing a systematic assessment of the scientific literature. Systematic reviews can have an enormous positive impact on global healthcare (27). For instance,

the systematic review on the use of corticosteroids for the prevention of premature births has been reported to have saved the lives of tens of thousands of people worldwide (28). However, Systematic reviews consist of a series of labor-intensive steps that are currently performed manually: first, a search strategy is designed; second, the scientific literature is searched using various search engines; the articles found are then screened and, finally, the information is extracted and assessed for quality using a grading system based on specialized checklists. So, carrying out a systematic review is a resource-intensive and complex activity (29), which is both expensive and time-consuming (30). Indeed, nowadays, a systematic review can cost anywhere between US$30,000 to US$300,000 and take one to two years to be completed (30). Several tools have been developed to facilitate the process of systematic reviewing by improving the management of the systematic review process, mainly by helping to organize data extraction and team coordination (29). This can facilitate crowdsourcing and optimize resources; however, many steps of the systematic review, such as article screening, still require enormous efforts (31). This problem requires industrial-scale cost-effective ways to search and synthesize evidence. (30).

Even though systematic reviews are the "gold standard" for synthesizing primary research, they are limited when it comes to answering the complex questions faced by clinicians in daily practice, for example, "what drugs could affect osseointegration in my patient?". Answering a question such as this one is currently unfeasible because it would require over 553 systematic reviews (one for each of the 553 drug categories defined in PubMed) that could translate to an estimated 620 years of work using traditional methods (30). Moreover, in fields in which data is sparse and patchily distributed or in which there is great variability in methodology, systematic reviews are not appropriate because it focuses on finding out the state of knowledge on a particular topic (4).

2.4 Evidence mapping review (EMR)

An Evidence Mapping Review is defined as a systematic search of a broad field to answer complex open questions and to identify gaps in knowledge for future research needs (4) This type of review was initially developed for fields with a limited number of publications, such as environmental sciences or education, and only provides information about the distribution of articles in a particular research area (30). Accordingly, the concept of subject-wide evidence synthesis was developed to combine systematic mapping strategies with systematic reviewing of the mapped articles. This approach could, for instance, help to map the entire medical literature as a function of disease and treatments. This type of map would help answer very complex questions, such as "what mediations can be used to treat diabetes?" or, "in a patient with diabetes, what medications are best?" However, the size of the healthcare scientific literature is enormous; thus, full systemic mapping and subject-wide evidence synthesis are usually not feasible (30). Indeed, previous efforts in subject-wide evidence synthesis have been very limited and rely on extensive crowdsourcing (30).

2.5 Machine Learning (ML) and Systematic Reviews

Machine Learning is a large sub-field of Artificial Intelligence (AI) that gives computers the ability to learn without being explicitly programmed (32). This means creating programs that have the ability to learn and do some intelligent activities outside the notion of programming.

ML tools can be used to accelerate the systematic review process by full or semi-automation of the different steps in a systematic review (33). Previous studies have shown that human effort can be reduced by using machine learning software to prioritize large reference collections, such that most of the relevant references are identified before screening is completed (34). Also, machine learning algorithms such as Robot-Reviewer can be used to appraise the quality of the scientific literature, a critical step in any systematic review (35).

As many as 44 different algorithms have been developed to automate screening of systematic reviews. These algorithms use natural language processing to estimate the probability of including or excluding an article (36). Some of these review tools, such as "Rayyan," train a machine learning classifier by promoting the abstracts that have more similar words to previously included abstracts (36). Others, such as the "Shiny R" application for ML article screening developed by the European Food Safety Authority (EFSA), rely on words or strings of words (37). RobotAnalyst combines text-mining and machine learning algorithms for organizing references by their content and actively prioritizing them based on a relevancy classification model trained and updated throughout the process (34).

ML has been used to perform broad/shallow systematic reviews achieving up to 98.7% sensitivity and 86% specificity; however, this requires very large training sets (i.e., up to 5,749 records) (31). Newer algorithms such as Abstrackr offers specificity that range between 0.69 - 0.90, a false negative rate of 3.5 - 21.2%, and a workload reduction of 6 - 67%, which is promising but still not good enough to replace human screening (33). Even though ML is considered safe and ready for use in 'live' reviews (38), it still faces many issues that need to be addressed. Machine learning algorithms are often based on the inclusion and exclusion of decisions made by humans. Thus, the main limitation of all ML algorithms for systematic reviews is a large number of human decisions needed to reach reliable results (36). Usually, substantial manual screening is needed to achieve relevant results (34), and most classifiers are only able to reduce the number of abstracts requiring manual screening by about 50% (39), saving only 30% to 70% of the workload (38). Another limitation is the relatively low reliability of such classifiers (36), the naive active learning-based screening process is biased in favor of selecting similar documents (40), and the saving in workload is accompanied by a best-case-scenario loss of 5% of relevant studies (i.e., a 95% recall) (38).

Therefore the use of ML is often limited to the exclusion of the most obvious articles, which constantly between 30% and 70% of the articles that need to be reviewed in the most systematic reviews (36).

Chapter 3: Osseointegration Pharmacology: A Systematic Mapping Using Artificial Intelligence

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3.1 Abstract

Introduction: there is growing evidence associating patient systemic conditions and medications to the success of osseointegrated medical devices such as dental implants and hip prosthesis. However, bibliographic assessment of these associations cannot be fully achieved with conventional systematic reviews due to the broad scope of the question addressed. Evidence mapping methods are better suited to such a task; however, evidence mapping can be very resource-intensive.

Artificial intelligence can be used to reduce the workload associated with systematic reviews and systematic mappings. However, the available methods are limited in their ability to reduce the workload and their sensitivity and specificity. A limiting factor is the quality of the training datasets used for machine learning.

Hypothesis: systematic mapping of the effect of medications on bone-implant osseointegration can be successfully achieved using a machine learning (ML) algorithm trained with similar and non-similar training datasets.

Objective: the objective of this study was to develop a method for Systematic mapping of the literature using a machine learning (ML) algorithm trained with similar and non-similar training datasets and use this to identify the effect of medications on bone-implant osseointegration.

Methods: to produce high-quality training datasets for machine learning, we conducted precise search strategies to produce similar and non-similar articles using PubMed. The articles were screened manually and classified into include and excluded articles. The inclusion criteria were clinical and animal studies that assessed the effect of systemic medication on bone-implant osseointegration.

The dataset of included and excluded articles screened manually were used to train a machine-learning algorithm based on Support Vector Machines. The algorithm produced was validated against a published systematic review with a search strategy that falls within the scope of ours. Then, the trained algorithm was used to screen articles identified with a highly sensitive search strategy (543927 articles).

Results: our algorithm was able to screen half-million published articles and reduce the workload by 95% with an accuracy of 95%, a False Positive Rate (TFP) of 95%, a sensitivity of 93%, and a specificity of 95%. The number of articles retrieved and included for the final analysis was 268 articles. In these articles, we identified 31 drug families that have been studied for their effect on osseointegration.

Conclusion: partial automation of systematic mappings can be successfully achieved with similar and non-similar training datasets classified by MeSH-terms. This method allowed us to perform a systematic mapping on the effect of medications on bone-implant osseointegration, and we identified 31 drugs that affect osseointegration.

3.2 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 (41), and about 100,000-300,000 dental implants are and over 96,000 cochlear implant devices are placed in the United States every year (42-44). 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 (20). Recent studies have shown that some pharmacological agents could affect osseointegration and implant survival by interfering with the pathways that regulate bone metabolism and healing (45). This is becoming an issue since a large portion of patients treated with osseointegrated devices suffer from diseases or conditions that require them to take medications (46).

Identifying all drugs known to affect osseointegration in the literature could help make better informed clinical decisions and guide researchers towards identifying knowledge gaps related to the effect of pharmacological agents on osseointegration (4). However, complex open questions such as “what drugs affect osseointegration?” are too extensive for a conventional systematic review to address. Evidence mapping reviews were developed to address this type of questions (4). This approach consists of mapping the entire medical literature for abroad medical questions

and visualize a thematic area to establish what the researchers know and do not know about the effects of an intervention. However, the size of the healthcare scientific literature is enormous; thus, full systemic mapping and subject-wide evidence synthesis are usually not feasible (30). Indeed, previous efforts in subject-wide evidence synthesis have been limited because they need to rely on extensive crowdsourcing (30).

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 (30, 33). Indeed many different machine learning (ML) algorithms have been developed to automate screening of systematic reviews (47). 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 (36). However, most of the algorithms require very large training datasets (i.e., up to 5,749 records) (31), and they are only able to reduce the number of abstracts requiring manual screening by about 50% (39), saving only 30% to 70% of the workload (38).

Very recently, ML has also been used for fully or semi-automated evidence mapping reviews. For example, Juleen Lama et al. published an evidence mapping review on the effect of low-calorie sweeteners (LCS) on health outcomes (5). This mapping review used a semi-automated machine learning approach to tag and categorized the included articles. However, they had to screen 28% of their articles in order to train their algorithms. Also, the clinical search engine Tripdatabase.com has developed an artificial intelligence (AI) for full automation of evidence mapping (6). 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 (6).

The performance of an AI for text mining depends on the quality of the training datasets and the text used for mining (48). Unfortunately, the 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.

We could 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 a particular type of Artifical Intelligence based on "natural language understating" to generate high-quality MeSH terms (49). 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 (50).

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 for systematic mappings. This classifier used MeSH terms and training datasets with similar and non-similar articles.

3.3 Materials and Methods

3.3.1 Study design

As figure 1 shows, this study involves four main steps; manual articles screening, ML articles screening, validation of algorithm, and evidence synthesis. This evidence mapping adhered to the PRISMA-Extension for Scoping Reviews (51), and it was carried out according to the methodology of Global Evidence Mapping (GEM) (52), adding suggested components from Ballesteros, Mónica et al. (53). 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 a highly 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 descriptive map of the included studies involved in-depth syntheses, which assessed study design, drug name, type of study, type of implant, drug doses, route of drug administration, study measurements, and study outcomes (i.e., the effect of the drugs on osseointegration) and the study quality.

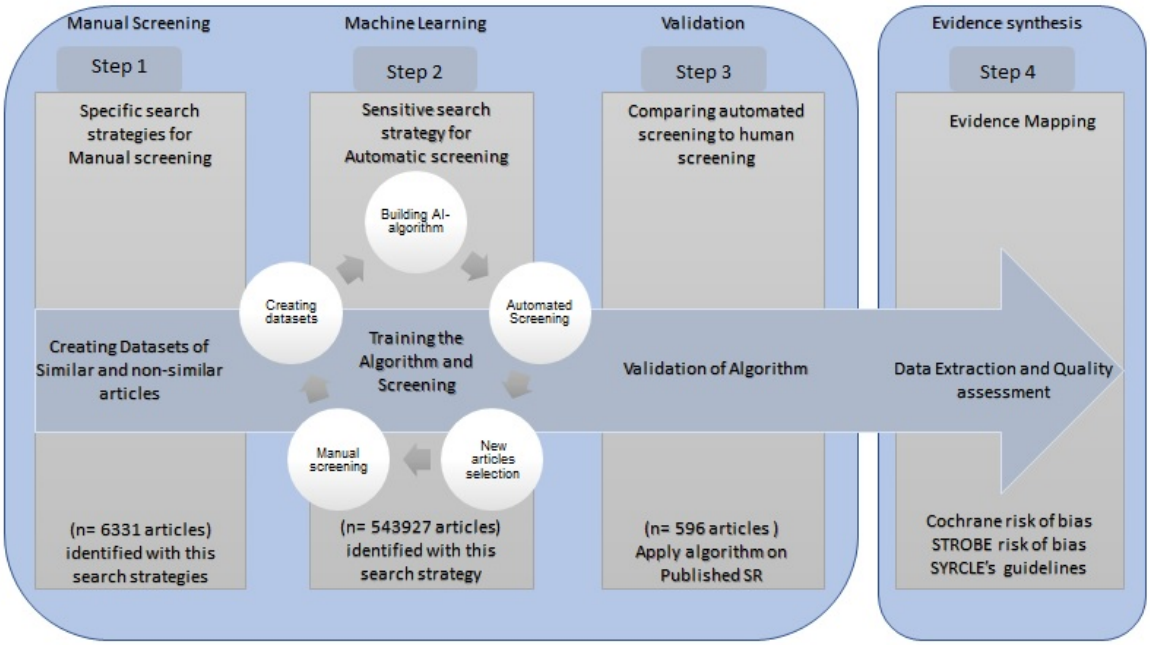

Figure 1: Workflow diagram showing the steps of our Evidence Mapping Review using Machine Learning

3.3.2 Search strategy (step 1 and 2)

In this evidence mapping, an electronic search of the MEDLINE databases through the PubMed interface was performed on July 1, 2018, using three different search strategies, as described in Table 1 and also complementary data is available in Appendix A:

- Search strategy A: a specific search strategy that was designed to obtain similar articles. This search strategy was very specific and focused solely on the MeSH-term “osseointegration/drug effects.”
- Search strategy B: a specific search strategy that was designed to obtain non-similar articles. This search 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: a highly sensitive search strategy designed to obtain all articles related to osseointegration. This search strategy was designed to identify all relevant articles. However,

it retrieved many irrelevant studies as well, and it could substantially increase the workload if the screening were to be done manually.

Table 1: Search strategies used in the systematic mapping

Search Method	Pub-Med MeSH terms	Date of Search
A- Precise Search Strategy for similar articles	"Osseointegration/drug effects"[MeSH Terms]	July 2018
B- Precise Search Strategy for non-similar articles	("Dental Implants"[Mesh]) AND ("Pharmacological action Category ")	
C- Highly Sensitive Search Strategy	("Dental Implantation, Endosseous"[Mesh]) OR ("Dental Implants"[Mesh]) OR ("Osseointegration"[Mesh]) OR ("Periprosthetic Fractures"[Mesh]) OR ("Drug Implants"[Mesh]) OR ("Internal Fixators"[Mesh]) OR ("Hip Prosthesis"[Mesh]) OR ("Prostheses and Implants"[Mesh]) OR ("Implants, Experimental"[Mesh] OR "Bone Screws"[Mesh]) OR ("Prosthesis Implantation"[Mesh])	

3.3.3 Eligibility criteria (step 1 and 2)

We included articles published until July 1, 2018, assessing the effect of drugs on bone-implant osseointegration in human subjects as well as in 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, and osteonecrosis.

3.3.4 Screening Method (step 1 and 2)

Screening of articles obtained with the specific search strategies A and B was done manually by two independent calibrated reviewers (MM, AD) according to our inclusion and exclusion criteria (Figure 3). Disagreements between the two 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.

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

A script was created in Python to extract the metadata from the included and excluded articles that were screened manually using specific search strategies. The metadata extracted from PubMed included title, abstract, keywords, and MeSH-terms.

The articles classified as 'included or excluded' were used to train a machine-learning algorithm using the software Waikato Environment for Knowledge Analysis (WEKA) developed at the University of Waikato, New Zealand (54). Weka is a widely used open-source machine learning platform that allows us to test, build, and compare different machine learning models (55). We used a support vector machine (SVM) algorithm due to its well-established effectiveness in text mining (56). 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 currently produced by PubMed use a natural language understanding AI that incorporates very relevant semantic value to the terms (49).

During the manual screening process, most articles were excluded, and only a small portion was included. This skewing of data resulted in an imbalance in the training dataset (i.e., a high

proportion of irrelevant papers), which in turn impaired the performance of the ML classifier (37). 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 (34). Clustering was also used to provide a more coherent organization than topic modeling (34).

The algorithm obtained with the training datasets described above was used for automated screening of the 543927 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 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).

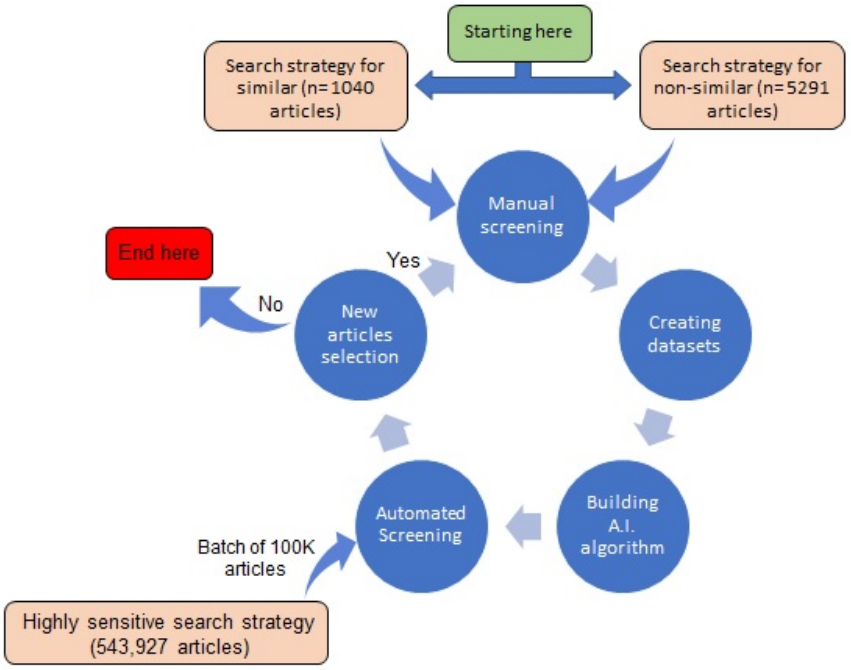

Figure 2: Workflow diagram showing the process of screening the literature in our systematic mapping.

3.3.6 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 (3). The included and excluded articles in this previously published systematic review were kindly provided by the authors (Table 2) and used to test our algorithm and estimate its accuracy, sensitivity, and specificity.

3.3.7 Data Extraction (step 4)

After study selection, the following general characteristics were extracted from each included article: first author's surname, study design, drug name, type of study, mean age, gender, sample size, type of implant, drug doses, route of drug administration, follow-up time, measurements, outcome, geographical location, year published and reference; complementary data is available in Appendix B.

To identify the research questions of each study, we used the PICO framework, which specifies the four key elements; population, intervention, comparison, and outcomes (57). We only considered the articles in which the research question and all the elements of the PICO framework were provided, and a conclusion of the drug effects on bone-implant osseointegration was clearly described. The population and animal characteristics (e.g., gender, mean age, and implants location), the intervention (e.g., drug type, drug doses, route of drug administration), comparison (such as placebo), and measurements (implant survival, bone-implant contact, implant push-out test, implant pull-out test, peri-implant bone volume, and force-torque test) and the outcomes were extracted in details; complementary data is available in Appendix B.

The conclusions of the included articles were divided into three categories depending on the outcome, similarly to previous studies (53). If the conclusion of the included articles showed clearly and in an indicative language without major concerns regarding the existing evidence 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 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 showed clearly and in indicative language that the drug showed no effect, not negative or no positive effect on bone-implant osseointegration, we considered the outcome as "no effect."

3.3.8 Quality assessment and risk of bias (step 4)

Two reviewers assessed the methodological and reporting 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 (58), clinical trials were assessed using Cochrane risk of bias tool for randomized controlled trials (59), and the STROBE quality assessment tool was used for the observational studies (60).

3.3.9 Evidence mapping presentation (step 4)

The demographic characteristics of the included studies, methodology, measurements used to analyze osseointegration, and the main outcomes and the quality assessment were described on tables. We performed a narrative description for the included studies, including study design, type of implant, drug name, doses, and route of administration, and specific outcome. 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 on STROBE assessment and Cochrane risk of bias for human clinical subjects and SYRCLE’s guidelines for animal studies as “poor,” “fair,” “good”; and 3) the number of studies included for each drug was represented by the bubble size.

3.4 Results

3.4.1 Study Selection

The similar specific search strategy identified 1040 articles, the non-similar specific search strategy identified 5291 articles, and the highly sensitive search strategy identified 543927 articles. The 6331 articles identified with similar and non-similar specific search strategies were screened manually. From those articles, 250 articles were selected for full-text assessment studies, 155 were included, and 6176 were excluded. The datasets of included and excluded articles were then used to train a machine-learning algorithm. The trained algorithm was then used to screen the articles identified with the highly sensitive search strategy (543927 articles). Eventually, a total of 268 included studies were finally selected. The Flow diagram in figure 3 represents the study selection process.

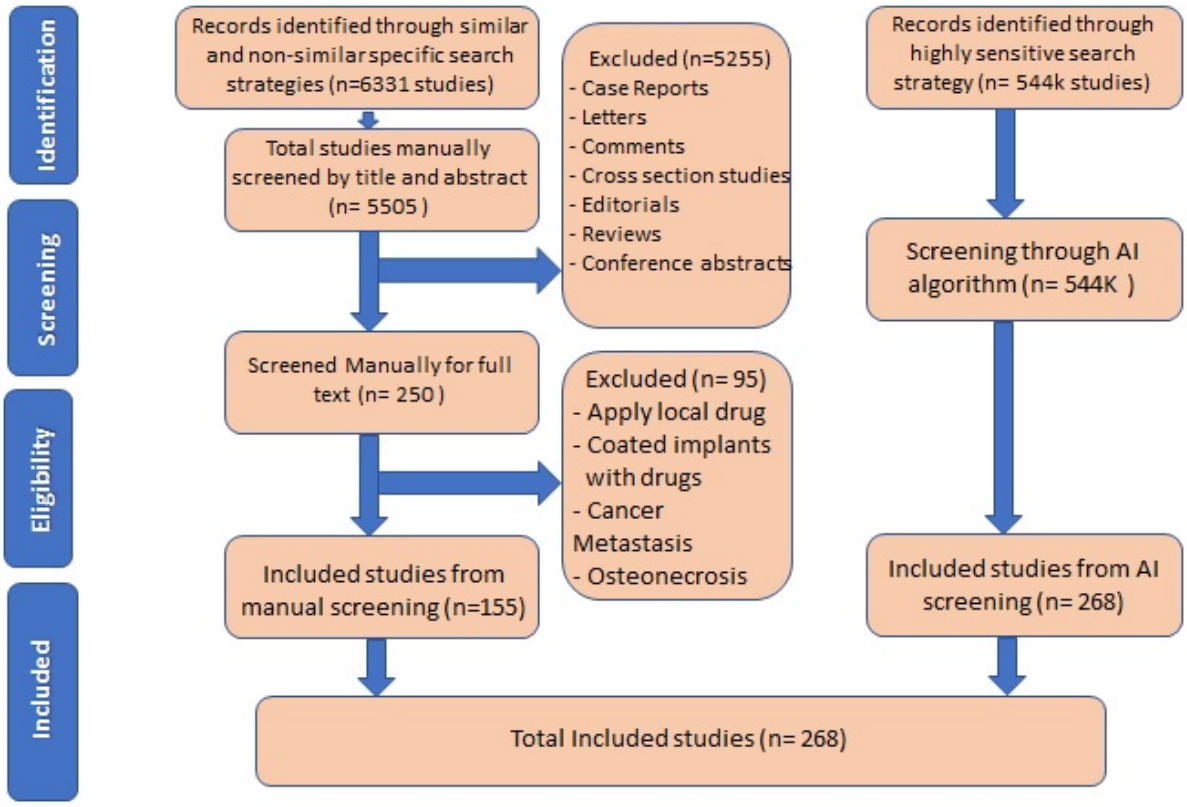

Figure 3: Flow diagram of the study selection process.

3.4.2 Building the algorithm and improving its selection performance

As described in Figure 4, the initial performance of the algorithm presented a low rate of true positive selection; however, after each reiteration, the size of the training datasets increased, and the algorithm performance improved. The training dataset was progressively increased until reaching a threshold beyond which the algorithm was not able to identify any new articles. This was achieved by screening 8121 articles, 1.49% of the total dataset. We were screening all articles twice in two subsequent rounds until reaching the plateau.

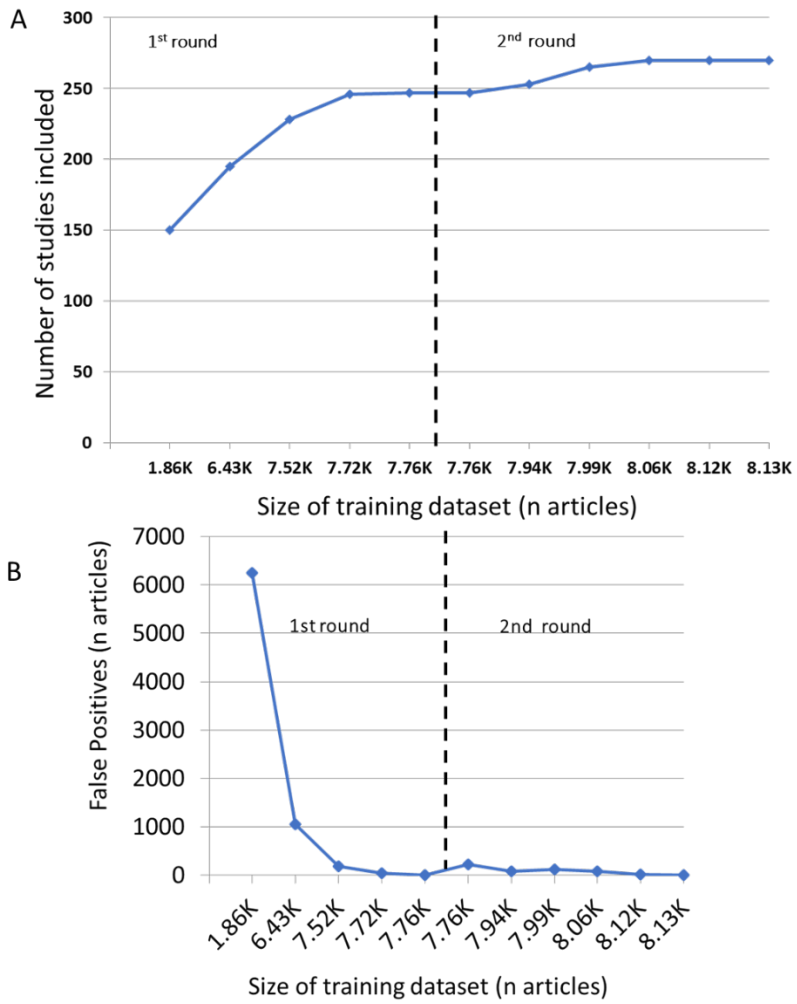

Figure 4: Performance of the algorithm as a function of the training dataset. A: Graph depicting the number of articles included as a function of the size of the training data set. As the size of the training datasets increased, the number of included articles identified by our algorithm also increased. Reaching a plateau at 268 articles with a training dataset of 8.12k articles, then the algorithm was ready to be applied. B: Graph depicting the number of false-positive articles as a function of the size of the training data set. The selection of false-positive articles decreased exponentially as the size of the training dataset increased. Through the second screening (Re-Run, 2nd round) of our dataset, we were able to reduce false-positive articles from 6449 to 20 articles.

3.4.3 Performance of the algorithm

The initial performance of the algorithm presented a high rate of false-positive; however, after each reiteration, the performance improved until reaching a very high recall and precision, Figure 4.

3.4.4 Validation of the method for data screening

With a previously published systematic review, 17/596 articles were a part of the selected articles in this published systematic review. AI was able to identify 13/17 of all relevant articles with an accuracy of 95%, a False Positive Rate (TFP) of 95%, a precision of 30%, a sensitivity of 93%, and a specificity of 95%. Also, the algorithm has the ability to reduce the workload up to 95%, Table 2. However, the AI correctly discarded 3/17 articles because they did not meet our inclusion criteria which is our training datasets, one article was about case reports, second was about osteoporosis and bisphosphonate-related osteonecrosis, third was about analysis of risk factors for cluster behavior, and one incorrectly discarded as a false negative.

Table 2: Validation of the algorithm

Validation of Algorithm Using a Published Systematic Review	
True positives (TP)	13
False negatives (FN)	1
True negatives (TN)	551
False Positives (FP)	31
False Positive Rate (FPR)	95%
Workload reduction	95%
Sensitivity	93%
Specificity	95%
Accuracy	95%
Precision	30%

We validated our algorithm against a published systematic review in which 596 articles were screened and 14 RCT and observational studies were included.

The AI screening method identified 268 articles of the 543927 articles retrieved from the highly sensitive search strategy. This includes the 155 articles retrieved from the manual screening of the articles retrieved with the specific search strategies and another 113 articles that were only

identified using our AI screening methods, Figures 5 and 6. Among the included studies, there were 192 animal studies and 76 human subjects' studies, Figures 10, 11, and 12. The animal and human studies assessed 31 drugs. Among these, 29 drugs were investigated in animals, and 14 drugs were studied in humans.

The quality assessment of the studies was stratified according to the drug category and type of study. RCTs on NSAID, Bupivacaine without vasoconstriction, 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 7 and also complementary data is available in Appendix E). For observational studies on Bisphosphonate, NSAID, Chemotherapy, Parathyroid hormone replacement therapy, Vitamin D, Xianlinggubao, Thyroid hormone replacement therapy, and Antibiotic (Penicillin) presented high to moderate risk of bias, studies on Antihypertensives, SSRI, Statins, and PPI presented low to moderate risk of bias, and Corticosteroid, Testosterone hormone replacement therapy, and Estrogen hormone replacement therapy presented moderate risk of bias (figure 8 and also complementary data is available in Appendix F). For animal studies, those assessing Bisphosphonate, NSAID, Chemotherapy, Immunosuppressive therapy, Sex hormone replacement therapy, Statin, Aprotinin, Thyroid hormonal replacement therapy, Parathyroid hormone replacement therapy, 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 9 and also complementary data is available in Appendix C). Studies on Proton-Pump Inhibitor (PPI), Aprotinin, and Anti-vascular

endothelial growth factors (VEGF) presented low to moderate risk of bias (figure 9 and also complementary data is available in Appendix C).

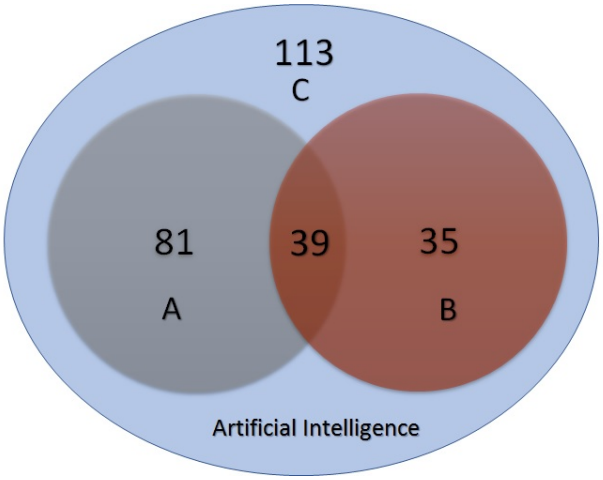

Figure 5: Venn diagram showing the number of articles identified with each screening method and search strategy. A- represents the articles screened manually from the specific search strategy for similar studies, B- represents the articles screened manually from the specific search strategy for non-similar studies, C- represents the new articles screened by AI from the highly sensitive search strategy.

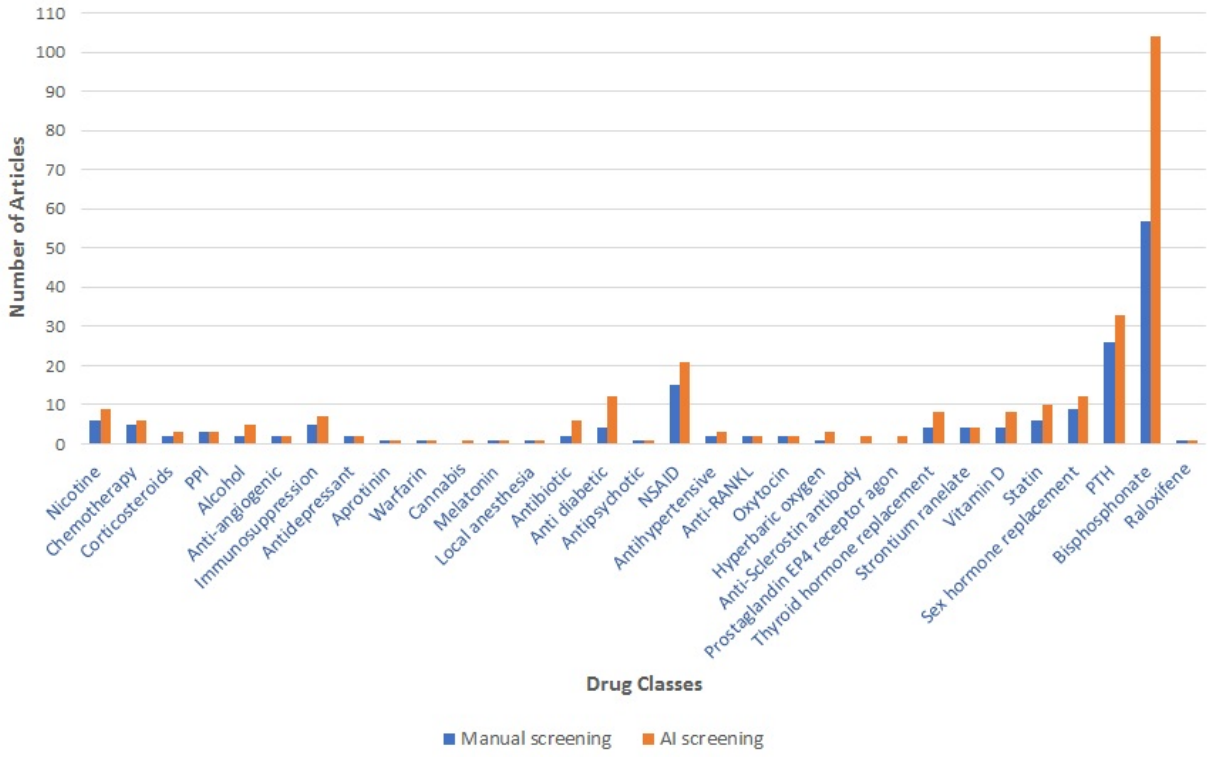

Figure 6: Number of studies included for each drug as a function of the screening methods (A.I. or manual screen).

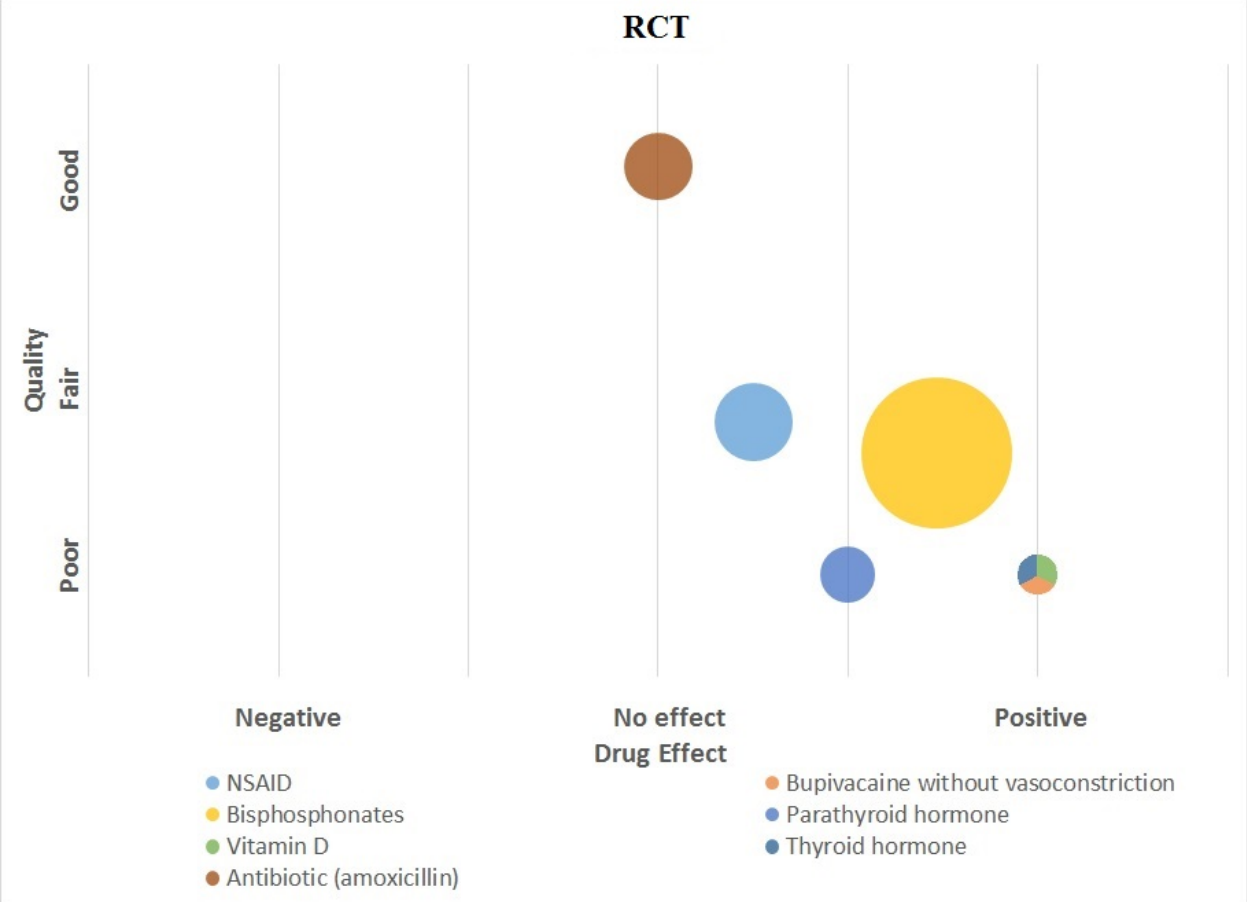

Figure 7: Bubble plot for RCT representing the number of studies per drug, the quality of the studies, and the effect of the drugs on osseointegration for each study. The y-axis represents the quality of the study according to the risk of bias tool. The x-axis notates the drug effect on osseointegration. 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 different drugs that have the same number of studies, the same quality, and the same effect on osseointegration.

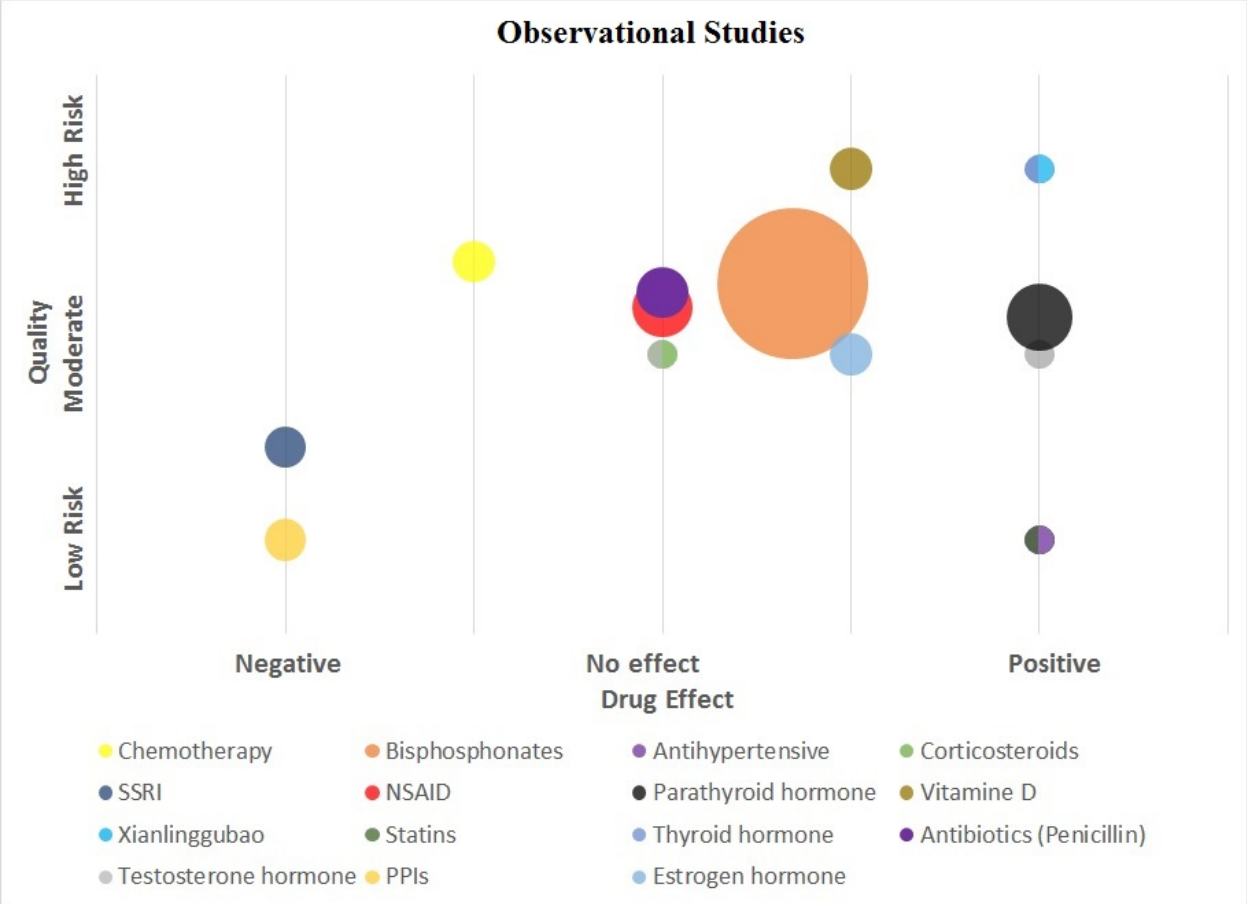

Figure 8: Bubble plot for observational studies representing the number of studies per drug, the quality of the studies, and the effect of the drugs on osseointegration for each study. The y-axis represents the quality of the study according to the risk of bias tool. The x-axis notates the drug effect 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 different drugs that have the same number of studies, the same quality, and the same effect on osseointegration.

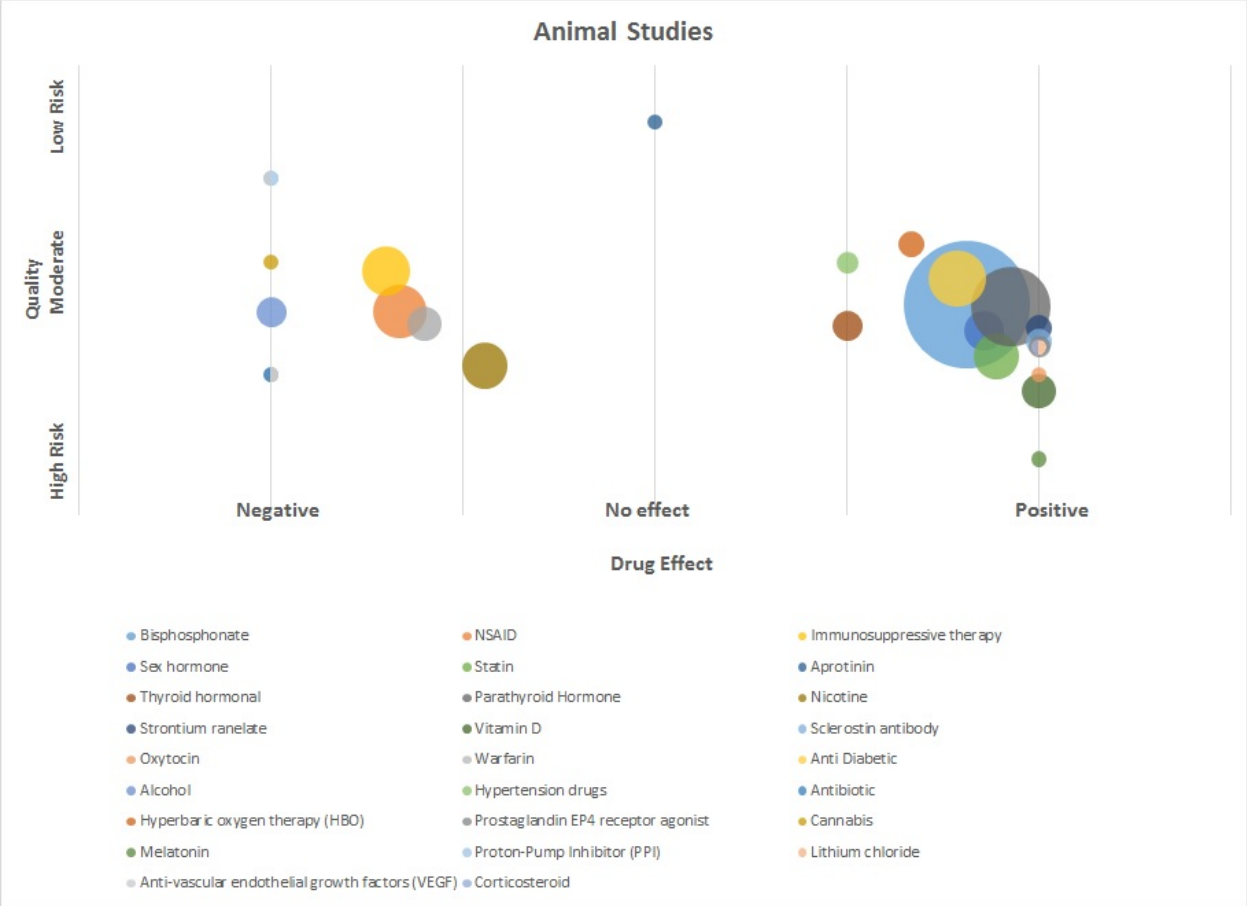

Figure 9: Bubble plot for animal studies representing the number of studies per drug, the quality of the studies, and the effect of the drugs on osseointegration for each study. The y-axis represents the quality of the study according to the risk of bias tool. The x-axis notates the drug effect on osseointegration. 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 different drugs that have the same number of studies, the same quality, and the same effect on osseointegration.

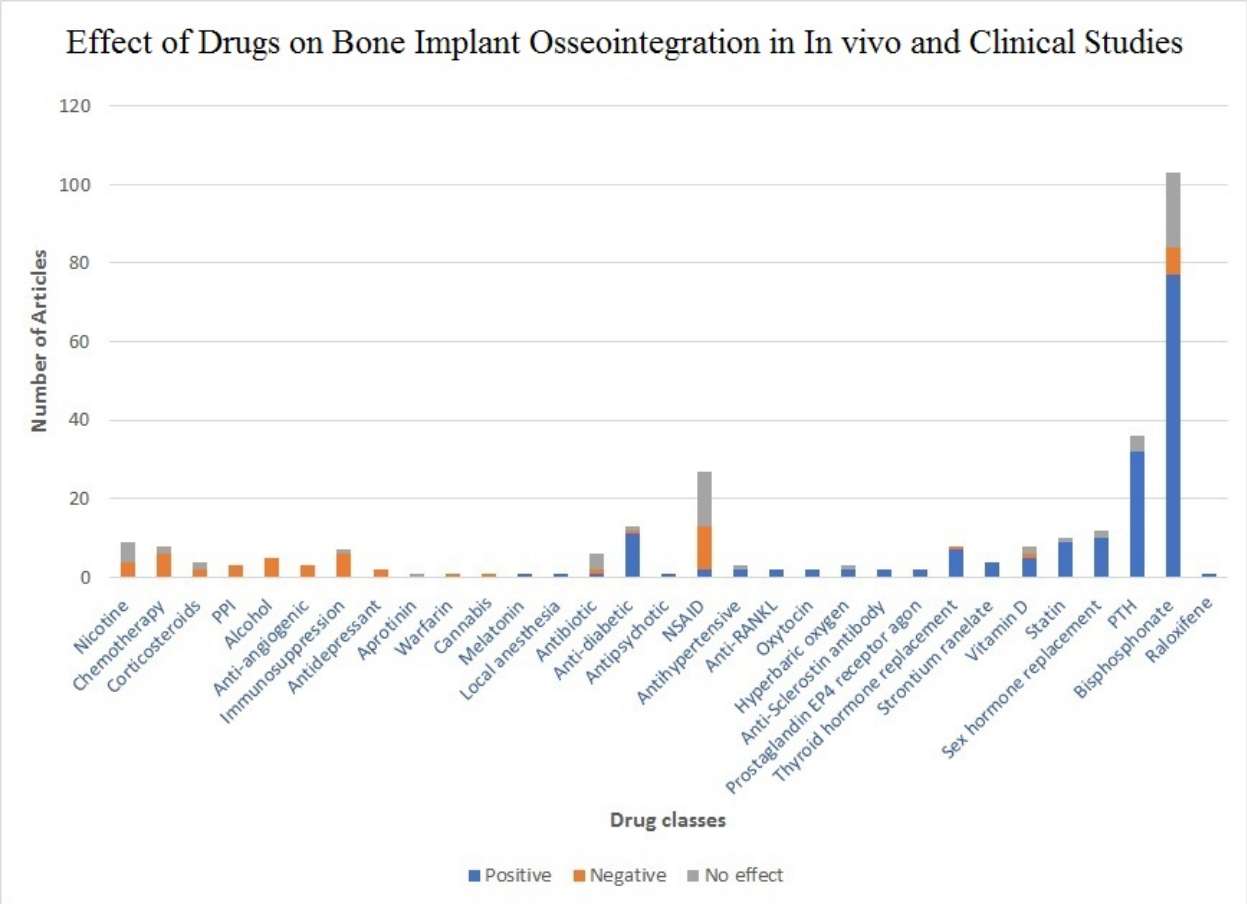

Figure 10: The effect of drugs on bone-implant osseointegration in the included in vivo and clinical studies

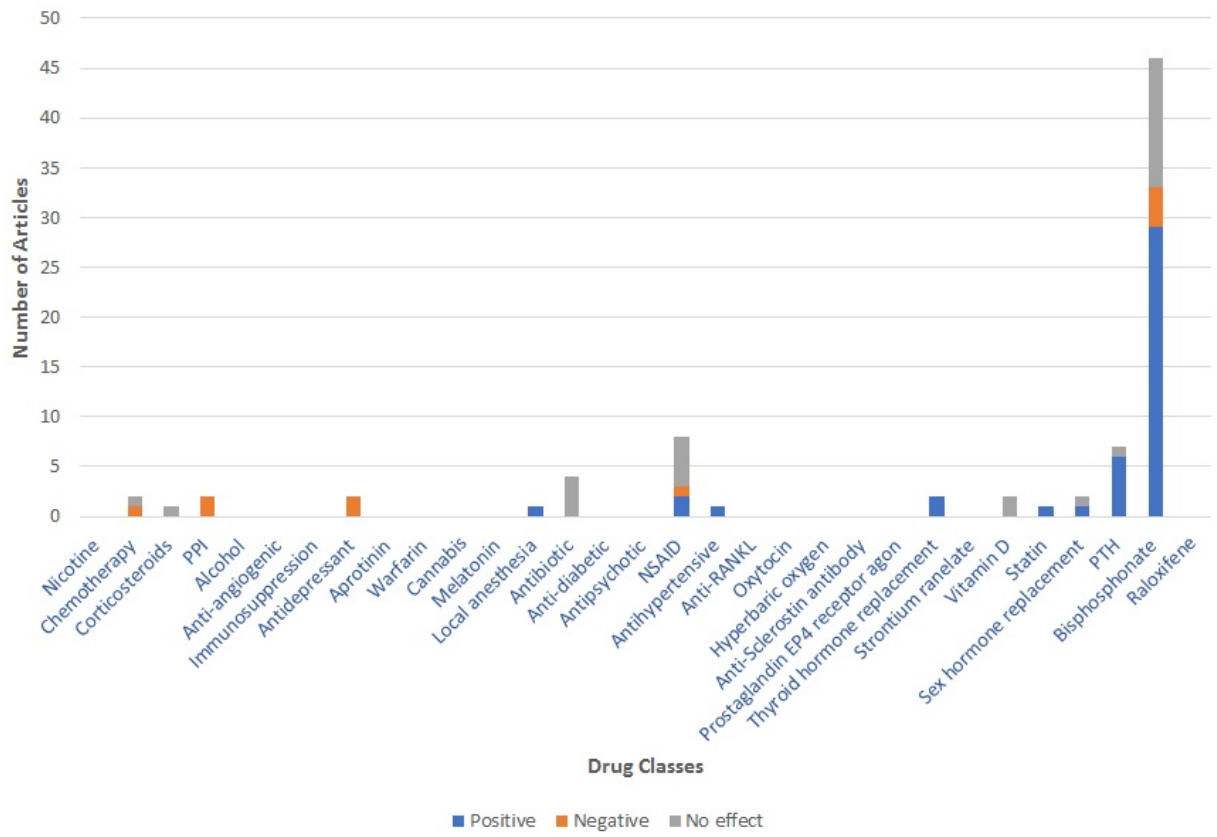

Figure 11: The effects of drugs on bone-implant osseointegration in the included clinical studies.

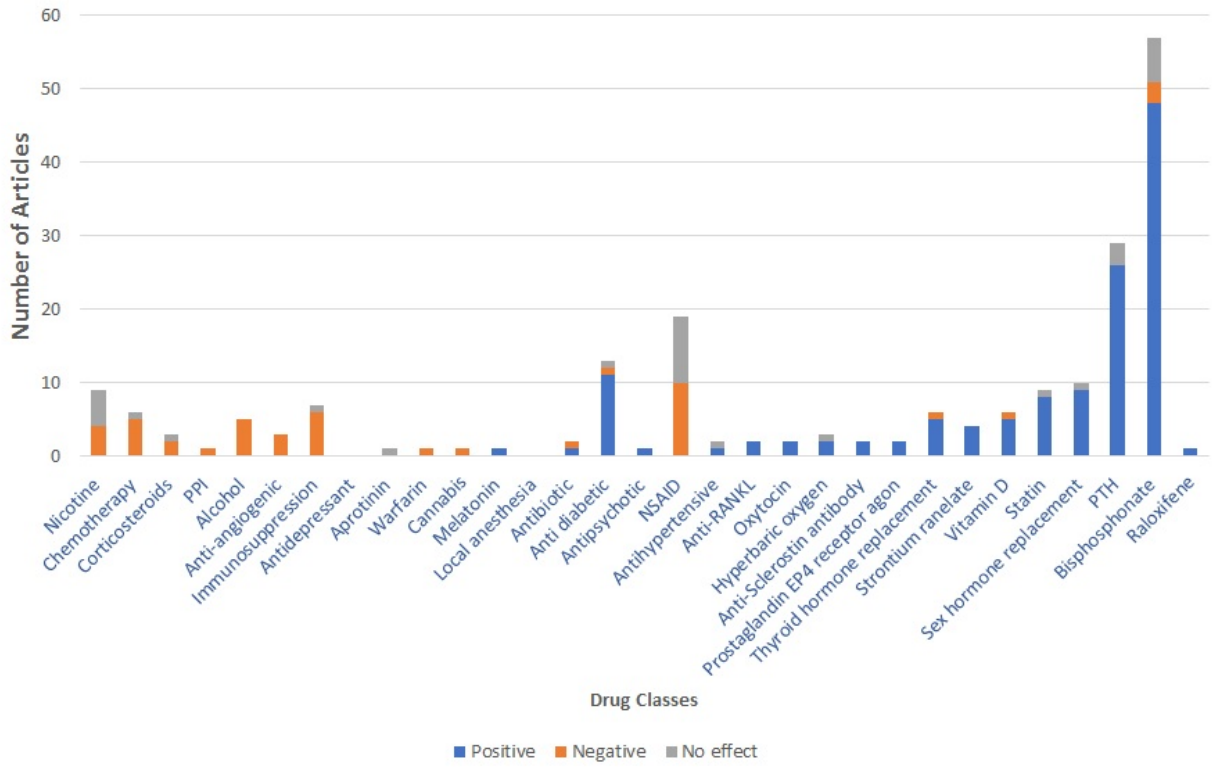

Figure 12: The Effects of drugs on bone-implant osseointegration in the included in vivo studies

Table 3 summarizes the number of articles identified per drug category as a function of the screening methods used to identify the study, the type of study, and the study outcome regarding the effect of the drug on osseointegration. Two hundred sixty-eight studies were included in this review (Table 3) and were identified by the highly sensitive search strategy using A.I. Only one hundred fifty-five of these articles were identified with specific search strategies using manual screening. Out of this, thirty-one drug categories were identified, and eight of these drugs were also used in combination with other drugs as (Table 3 and Figures 6, 10, 11,and 12).

3.4.5 drugs effects on bone-implant osseointegration:

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

3.4.5.1 Anti-osteoporosis Drugs

3.4.5.1.1 Bisphosphonate

Different bisphosphonate medications have been assessed for their impact on bone-implant osseointegration these include alendronate, disodium diphosphonate, zoledronic acid, risedronate, TRK-530, YM-175, pamidronate, ibandronate, clodronate, etidronate, and tiludronate. The use of unspecified doses of bisphosphonates was associated with a low risk of implant failure in four cohort studies, two of these were retrospective studies on total knee and hip arthroplasty, one was a retrospective study on total knee arthroplasty, and one was a prospective study on lumbar fusion (61-64). However, the use of unspecified doses of bisphosphonates was associated with a high risk of implant failure in one retrospective cohort study on dental implants (65). On the other hand, the use of unspecified doses of bisphosphonates had no significant effect on implant failure in six retrospective cohort studies on dental implants (66-71). Underneath, we discuss the literature on the specific types of bisphosphonates.

3.4.5.1.1.1 Zoledronic Acid

In human studies , use of zoledronic acid (4 and 5 mg) was associated with a 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 (72-74). However, a dose of 5 mg had no significant effect on implant failure in one prospective study on dental implants (75).

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) was found to have a positive effect on osseointegration (76-88). Five studies were on rats (four of them on ovariectomized rats), six studies on rabbits (three 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. Bone-to-implant contact, peri-implant bone volume, removal torque force test and push-out force test analyses showed that systemic administration of zoledronic acid improved BIO.

On the other hand, pre-operative and post-operative intravenous administration of zoledronic acid (0.0075-0.1 mg/kg/every 0.5-4 weeks) was found to have a negative effect on osseointegration in four animal studies (89-92). Two of these studies were on dogs, one on rabbits, and one on sheep. Three of these studies used screw titanium implants, and one used Hydroxyapatite (HA)-coated titanium implants. Bone-to-implant contact and peri-implant bone volume analyses showed that zoledronic acid impaired BIO.

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 (93, 94), 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 have a negative effect on osseointegration in one study on rabbits (92). 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 (94). 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 have a positive effect on osseointegration in one study on rabbits (95).

3.4.5.1.1.2 Alendronate

In human studies, use of alendronate (5-35 mg/day, or 70 mg/once a week) was associated with low risk of implant failure in one retrospective study on total knee arthroplasty, two prospective studies on total hip arthroplasty and total knee arthroplasty, respectively, and eleven Randomized Control Trials (two double-blinded, and two single-blinded); among the RCTs, nine were on total hip arthroplasty, and two were on total knee arthroplasty (96-109). Also, the use of alendronate (70 mg/once a week) combined with Xianlinggubao (phytoestrogen-rich natural product) (three times a day) was associated with a low risk of implant failure in one Randomized Control Trial on total hip arthroplasty (110).

However, the use of alendronate (4, 6, or 10 mg/day) was associated with a high risk of implant failure in two retrospective cohort studies on dental implants (111, 112).

The use of alendronate (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 (113-116).

In animal studies, pre-operative 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 have a positive effect on osseointegration in twenty five animal studies (76, 117-141). Twenty-one studies on rats (twelve of them on ovariectomized rats), two on dogs, two studies on rabbits (one of them on ovariectomized rabbits and one on non-ovariectomized rabbits), and one on pigs. Seventeen of these studies used titanium implants (9 screws, 3 Hydroxyapatite (HA)-coated, 4 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 one did not mention the type of implants. Bone-to-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 subcutaneous administration of alendronate (1 mg/kg/twice a week) was found to have a negative effect on osseointegration in one animal study on rats (142). This study used custom made titanium implants, and it showed that alendronate impaired bone-to-implant contact.

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 (143-148). 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 on BIO.

3.4.5.1.1.3 Disodium Diphosphonate

In animal studies, postoperative subcutaneous administration of disodium diphosphonate (0.1-5 mg/kg/day) was found to have a positive effect on osseointegration in one animal study on rabbits (149). This study used porous titanium fiber-mesh implants, and it showed that disodium diphosphonate improved bone-to-implant contact and peri-implant bone volume.

3.4.5.1.1.4 Ibandronate

In animal studies, postoperative subcutaneous administration of ibandronate (1.0-25 μg/kg/day or 700 μg/kg/single dose) was found to have a positive effect on osseointegration in five studies on rats (one of them ovariectomized rats) (150-154). These studies used hydroxyapatite (HA)-coated titanium implants, and they showed that ibandronate enhanced bone-to-implant contact and peri-implant bone volume.

3.4.5.1.1.5 Clodronate

In human studies, use of clodronate (100, 400, and 1600 mg/kg/daily) was associated with a 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 (155-157).

In animal studies, postoperative subcutaneous administration of clodronate (0.12, and 21 mg/kg/3 times a week) was found to have a positive effect on osseointegration in one animal study on rats using titanium plates (123). This study showed that clodronate enhanced bone-to-implant contact.

3.4.5.1.1.6 Risedronate

In human studies, use of risedronate (2.5 or 35 mg/kg/daily or 35 mg/kg/once a week) was associated with a 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 (99, 158-160).

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 (161). Moreover, **in animal studies**, pre-operative and postoperative subcutaneous administration of risedronate

(0.1 mg/kg/once every two days) was found to have a positive effect on osseointegration in one animal study on ovariectomized rats using screw titanium implants (124). This study showed that risedronate enhanced bone-to-implant contact and push-out test analyses.

3.4.5.1.1.7 Pamidronate

In human studies, the use of pamidronate (90 mg/kg) was associated with a low risk of implant failure in one double-blind Randomized Control Trial on total hip arthroplasty (162). Moreover, **in animal studies**, postoperative subcutaneous, Intramuscular, and intraperitoneal administration of pamidronate (0.4, 4, 40, and 500 μg/kg/daily, and 0.6 mg/kg/three and five times a week) was found to have a positive effect on osseointegration in five animal studies (four on rats, and one on dogs). (163-167). Three of these studies used screw titanium implants, one used endotoxin-coated polyethylene particles titanium implants, and one used stainless-steel screw-shaped implants. Bone-to-implant contact, peri-implant bone volume,pull-out test, and push-out test analyses showed that pamidronate enhanced BIO.

3.4.5.1.1.8 TRK-530 (Bisphosphonate)

In animal studies, post-operative subcutaneous administration of TRK-530 (1 mg/kg/every other day) was found to have a positive effect on osseointegration in one animal study on rats (168). This study used Kirshner (K)-wires, and it showed that TRK-530 improved bone-to-implant contact and reduced peri-implant osteolysis.

3.4.5.1.1.9 YM-175 (Bisphosphonate)

In animal evidence, pre-operative and post-operative subcutaneous administration of YM-175 (10 μg/kg/three times a week) was found to have a positive effect on osseointegration in one animal

study on ovariectomized rats (169). This study used screw-form titanium implants, and it showed that YM-175 improved bone-to-implant contact and reduced peri-implant osteolysis.

3.4.5.1.1.10 Etidronate

In human studies, use of etidronate (400 mg/kg, a day) was not found to be a contributing factor on implant survival rate in one double-blind Randomized Control Trial on total hip arthroplasty (170).

3.4.5.1.2 Parathyroid Hormone Replacement Therapy (PTH)

Different doses of parathyroid hormone replacement therapy (20 μg/kg/daily or 56.5 μg/kg/once a week, injection) have been assessed for their impact on bone-implant osseointegration.

In human studies, use of parathyroid hormone replacement therapy (PTH) (recombinant human parathyroid hormone) had no significant effect on dental implant failure rate in one single-blinded open-label randomized controlled feasibility study (171). However, the use of PTH had a positive effect in one retrospective study on total knee arthroplasty, one Randomized Control Trial on total hip arthroplasty and four prospective studies, three of these were cohort studies on lumbar interbody fusion pedicle screws and one on total knee arthroplasty, (64, 160, 172-174).

In animal studies, pre-operative and post-operative subcutaneous administration of PTH (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) was found to have a positive effect on osseointegration in twenty six animal studies (87, 137, 164-166, 175-194). Fourteen of these studies were on rats (seven of them on ovariectomized rats), three on low protein diet rats, five on rats (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 (12 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 subcutaneous administration of PTH (2, 40 and 60 μg/kg/three times a week) was found to have 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 (195-197).

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, three times a week) had a positive effect on bone-implant osseointegration simvastatin (188, 189) . Also, in another study, PTH (40 μg/kg/day/three days a week, Sc) showed a positive effect on osseointegration on rats smoking nicotine. (191).

3.4.5.1.3 Vitamin D

In human studies, use of vitamin D (1 mg/day) was not associated with an increase in the survival rate of osseointegrated implants in two single-blinded Randomized Control Trials on total hip arthroplasty (101, 109).

In animal studies, pre-operative and post-operative intraperitoneal, oral and subcutaneous administration of vitamin D (calcitriol) (0.1-60 μg/kg) had a positive effect on bone-implant

osseointegration in five animal studies (131, 198-201). Three of these studies were on ovariectomized rats, one on diabetic mice, and one on diabetic rats. Five studies used titanium implants (two screw-shaped, one unspecified design, one hydroxyapatite-coated, and one rod-shaped implants). Bone-to-implant contact, bone mass, pull-out force test, and push-out force analyses showed that systemic administration of vitamin D improved BIO under osteoporotic and diabetic conditions. Also, combining this drug with insulin (3.5 IU/twice a day, SC) resulted in improved BIO in one study on diabetic rats (198). Moreover, combining this drug with bisphosphonates (3.5 IU/twice a day, SC) also resulted in improved BIO in one study on ovariectomized rats (131).

On the other hand, one study on rats showed that vitamin D deficiency has a negative impact on BIO (202). This study used cylindrical hydroxyapatite-coated titanium implants, and it showed that vitamin D deficiency impaired bone-implant contact and peri-implant bone volume.

3.4.5.1.4 Anti-Sclerostin antibody

In animal studies, post-operative subcutaneous administration of sclerostin antibody therapy (25 mg/kg/twice a week) was found to have a positive effect on osseointegration in two studies on rats (203, 204). One of these studies used rod-shaped titanium implants, and the other one used cylindrical titanium implants. Bone-to-implant contact, peri-implant bone volume, and pull-out force test analyses showed that sclerostin antibody therapy improved BIO and might have the ability to limit the progression of established osteolysis.

3.4.5.1.5 Anti-RANKL

In animal studies, post-operative subcutaneous administration of anti-RANKL (OPG-Fc) (8-10 mg/kg/twice a week) was found to have a positive effect on osseointegration in two studies on rats

(130, 205). One of these studies used stainless-steel screw implants, and the other one used cylindrical titanium plate plugs. Bone-to-implant contact, peri-implant bone density, and the pull-out test analyses showed that anti-RANKL improved bone-implant osseointegration.

3.4.5.1.6 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 (76, 206-208).

3.4.5.2 Analgesics

3.4.5.2.1 NSAID

Different NSAIDs have been assessed for their impact on bone-implant osseointegration. This includes meloxicam, diclofenac sodium, aspirin, ibuprofen, celecoxib, indomethacin, naproxen, rofecoxib-A, flurbiprofen, and parecoxib.

In human studies, unspecified NSAIDs have been shown to have negative effects on the marginal bone around dental implants in one retrospective cohort study (209). However, on another retrospective cohort study, NSAID significantly increased the crestal bone levels around single-tooth hydroxyapatite-coated implants (210). Underneath, we discuss the literature on specific types of NSAID drugs.

3.4.5.2.1.1 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 (211, 212). 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 (213). 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.

3.4.5.2.1.2 Diclofenac sodium

In animal studies, post-operative intramuscular administration of diclofenac sodium (1.07 mg/kg twice a day or 30mg/kg/day) had a negative effect on bone-implant osseointegration in two studies on rats and in another one on rabbits (213, 214). One of these studies used cylindrical Hydroxyapatite (HA)-coated titanium implants, and the other one 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 bone-implant osseointegration in two other studies on rabbits (215, 216). These studies used cylindrical titanium implants, and cylindrical (HA)-coated titanium implants. Bone-to-implant contact, bone volume and pull out test analyses showed that diclofenac sodium had no significant effect on implant osseointegration.

3.4.5.2.1.3 Aspirin

In animal studies, post-operative subcutaneous administration of aspirin (17 or 34 mg/kg/day for 2, 4, and 8 weeks) had a negative effect on bone-implant osseointegration in one study on rabbits

(217). This study used porous-coated chrome-cobalt implants, and it showed that aspirin impaired bone-to-implant contact and bone ingrowth.

3.4.5.2.1.4 Ibuprofen

In human studies, use of ibuprofen (400 mg/kg, 3 times a day or 600 mg/kg, 4 times a 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 (218-220).

In animal studies, post-operative subcutaneous administration of ibuprofen (17 or 34 mg/kg/day for 2, 4, and 8 weeks) had a negative effect on bone-implant osseointegration in one study on rabbits (217). This study used porous-coated chrome-cobalt implants, and it showed that ibuprofen impaired bone-to-implant contact and bone ingrowth.

3.4.5.2.1.5 Celecoxib

In human studies, use of celecoxib (200 mg/ twice a day) was not associated with a higher risk of implant failure in two double-blind Randomized Control trials, one on total hip and the other one on knee arthroplasty (221, 222).

In animal studies, postoperative oral administration of celecoxib (3 mg/kg/day) did not show any effect on bone-implant osseointegration in one study on rabbits femora using cylindrical (HA)-coated titanium implants (216). On the other hand, postoperative oral administration of celecoxib (10 or 25 mg/kg/day) had a positive effect in reducing implant debris-induced inflammation in mice. This study used titanium wear debris to assess the host inflammatory response, and the analysis of implanted titanium debris showed that celecoxib prevented implant debris-induced osteolysis (223).

3.4.5.2.1.6 Indomethacin

In animal studies, pre-operative and post-operative subcutaneous administration of indomethacin (1-10 mg/kg/day) had a negative effect on bone-implant osseointegration in three animal studies, two on rabbits and one on ovariectomized rats (124, 217, 224). These studies used porous-coated chrome-cobalt implants, cylindrical titanium implants, and screw implants, respectively. Bone-to-implant contact, bone ingrowth, and push-out test analyses showed that indomethacin impaired bone-implant osseointegration. On the other hand, pre-operative and post-operative subcutaneous and oral administration of indomethacin (1 and 4 mg/kg/day) did not show any effect on bone-implant osseointegration in two studies on rabbits and dogs (225, 226). These studies used cylindrical titanium implants, and they showed that indomethacin did not affect bone-to-implant contact and peri-implant bone density.

3.4.5.2.1.7 Naproxen

In animal studies, post-operative oral administration of naproxen (110 mg/kg/day) did not affect bone-implant osseointegration in one study on rabbits (227). This study used a cylindrical titanium chamber, and it showed that naproxen had no effect on bone-to-implant contact and bone ingrowth.

3.4.5.2.1.8 Rofecoxib-A

In animal studies, post-operative oral administration of rofecoxib-A (12.5 mg/kg/day) had no effect on bone-implant osseointegration in one study on rabbits (227). This study used cylindrical titanium chambers, and it showed that rofecoxib-A did not affect bone-to-implant contact and bone ingrowth.

3.4.5.2.1.9 Parecoxib

In animal studies, post-operative subcutaneous administration of parecoxib (1.5 mg/kg/day) had no effect on bone-implant osseointegration in one study on rabbits (215). This study used

cylindrical titanium implants, and it showed that parecoxib did not affect bone-to-implant contact and bone ingrowth.

3.4.5.2.1.10 Flurbiprofen

In human studies, use of flurbiprofen (100 mg/twice a day) in the first year of implant loading was associated with lower risk of implant failure in one double-blind Randomized Control Trial (228). This study was used to assess the effect of oral flurbiprofen on osseointegrated dental implants.

3.4.5.2.2 Prostaglandin EP4 receptor agonist

In animal studies, post-operative subcutaneous administration of prostaglandin EP4 receptor agonist (ONO-4819) (15-30 μg/kg/twice a day) was found to have a positive effect on osseointegration in two studies on ovariectomized rats (229)(317). 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.

3.4.5.2.3 Cannabinoids

In animal studies, post-operative intermittent inhalation of marijuana (3 g of dried marijuana leaves) was found to have a negative effect on osseointegration in one study on rats (230). This study used screw-shaped titanium implants, and it showed that intermittent-marijuana impaired bone-to-implant contact and the bone area within the threads of the implants.

3.4.5.2.4 Local anesthesia: Bupivacaine

In human studies, use of bupivacaine without vasoconstrictor was associated with an increased survival rate of osseointegrated implants in one Randomized Control Trial (231).

3.4.5.3 **Anti-Psycholeptics Drugs**

3.4.5.3.1 Melatonin

In human studies, oral administration of melatonin had a positive effect on bone-implant osseointegration in one study of pinealectomized rats that assessed the effect of postoperative use of this drug on osseointegration of screw-form titanium implants (232). This study used a dose of 5 mg/kg/once a day for 8.5 weeks after implant placement, and it showed that oral melatonin improved bone-to-implant contact and peri-implant bone volume.

3.4.5.3.2 Lithium chloride

In animal studies, systemic administration of lithium chloride had a positive effect on bone-implant osseointegration in one study on ovariectomized rats that assessed the effect of postoperative use of this drug on osseointegration of cylindrical-shaped titanium implants (233). This study used a dose of 150 mg/kg/twice a day for three months after implant placement, and it showed that LiCl improved bone-to-implant contact, peri-implant bone volume, and implant push-out force.

3.4.5.4 Antidepressant:

3.4.5.4.1 Selective Serotonin reuptake Inhibitors (SSRIs)

In human studies, systemic administration of Selective Serotonin Reuptake Inhibitors (SSRIs) was associated with a higher risk of implant failure in two retrospective cohort studies. Although only one of them showed significant results (234, 235)**.**

3.4.5.5 Drugs Used in Addictive Disorders

3.4.5.5.1 Nicotine

Different doses of nicotine have been assessed for their impact on bone-implant osseointegration. **In animal studies**, subcutaneously injection of 1.25 -9 mg/kg was found to have a negative effect on osseointegration in four animal studies, while four other studies using doses either 0.37 – 0.93 mg/kg or 9, 15 or 85.2 mg/kg did not show any effect, and the only study assessing the effect of smoking nicotine found that it had a negative effect on osseointegration. Also, another study, smoking nicotine combined with PTH (40 μg/kg/day 3 days/week, Sc), showed a positive effect on osseointegration on 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 (191, 236-244).

3.4.5.5.2 Alcohol

Different doses of ethanol have been assessed for their impact on bone-implant osseointegration. **In animal studies**, oral administration of ethanol (10% -20%) for 3-4 weeks before implant surgery and 2-9 weeks after implant placement was found to have a negative effect on osseointegration in five studies on rats (241, 245-248). Three of these studies used hydroxyapatite-coated implants, and the other two used titanium screw or cylindrical titanium implants. The studies showed that ethanol impaired bone-to-implant contact and new bone formation around the HA implants. Moreover, in another study on rats combined daily administration of nicotine with 10% Gay Lussac ethanol showed a negative effect on osseointegration (241).

3.4.5.6 Systemic Hormonal Replacements Drugs

3.4.5.6.1 Sex Hormone Replacement

Different sex hormonal replacement medications such as 17β-estradiol and dihydrotestosterone have been assessed for their impact on bone-implant osseointegration.

In human studies, use of sex hormone replacement therapy was not associated with an increased survival rate of osseointegrated implants in one retrospective cohort study (249). Underneath we discuss the literature on the specific types of sex hormone replacement drugs.

3.4.5.6.1.1 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 (250). Also, the use of alendronate (70 mg/kg/once a week) combined with Xianlinggubao (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 (110).

In animal studies, pre-operative and post-operative subcutaneous administration of 17β estradiol (20 μg/kg/daily or 3 to 4 days a week) was found to have a positive effect on osseointegration in eight studies on ovariectomized rats (134, 136, 251-256) . Five of these studies used screw-form titanium implants, 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, 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 (169, 257). On of these studies used cobalt-chromium porous plugs and the other used screw-

form titanium implants and it showed that short-term, high-dose estrogen replacement hormone did not affect significantly the bone-to-implant contact, peri-implant bone ingrowth and the result of the pull-out test.

3.4.5.6.1.2 Dihydrotestosterone

In animal studies, pre-operative administration of dihydrotestosterone was found to have a positive effect on osseointegration in one study on rats (258). This study used cobalt-chromium-molybdenum implants, and the bone-to-implant contact and pull-out analyses showed that dihydrotestosterone improved bone-implant osseointegration.

3.4.5.6.1.3 Raloxifene

In animal studies, post-operative oral administration of raloxifene (1.0 mg/kg/day) was found to have a positive effect on osseointegration in one study on ovariectomized rats (132). This study used screw-shaped titanium implants, and it showed that raloxifene improved the bone-to-implant contact, the bone area within the threads of the implants, and the implant reverse torque force.

3.4.5.6.2 Thyroid Hormone Replacement

Different thyroid replacement hormone medications such as calcitonin and levothyroxine have been assessed for their impact on bone-implant osseointegration. Underneath we discuss the literature on the specific types of thyroid hormone replacement drugs.

3.4.5.6.2.1 Calcitonin

In human studies, use of calcitonin was associated with an increased survival rate of osseointegrated implants in two different studies (259, 260). This association was statistically significant in one prospective cohort study but was not significant in a Randomized Control Trial.

In animal studies, different doses of calcitonin have been also assessed for their impact on bone-implant osseointegration in four animal studies on ovariectomized rats (124, 133, 251, 252). These studies found that subcutaneous administration of different doses of calcitonin (2 -16 IU/kg/daily or once every 2 days) had a positive effect on osseointegration. Three of these studies used screw-form titanium implants, and the other one used cylindrical HA implants, and it showed that calcitonin improved bone-to-implant contact and the bone area within the threads of the implants. On the other hand, the intramuscular administration of calcitonin (2 IU/kg, daily) showed a negative effect on osseointegration in one study on rabbits (261). This study used screw-shaped titanium implants, and it showed that calcitonin impaired the initial phase of the bone healing process around the implants.

3.4.5.6.2.2 Levothyroxine

In animal studies, pre-operative oral administration of levothyroxine (0.4 IU and 0.18 IU) were found to have a positive effect on osseointegration in one study on rats (262). This study used screw-form titanium implants, and it showed that levothyroxine improved bone-to-implant contact.

3.4.5.6.3 Oxytocin

In animal studies, post-operative subcutaneous administration of oxytocin (1 mg/kg/day) had a positive effect on bone-implant osseointegration in one study on ovariectomized rats that assessed the effect of machined and grit-blasted rod-form titanium implants on bone-implant osseointegration. Bone-to-implant contact, peri-implant bone volume, and push-out force analyses showed that oxytocin improved BIO under osteoporotic conditions (263, 264).

3.4.5.6.4 Corticosteroids

Different corticosteroid drugs such as prednisolone, methylprednisolone, and glucocorticosteroid have been assessed for their impact on bone-implant osseointegration. Underneath we discuss the literature on the specific types of corticosteroid drugs.

3.4.5.6.4.1 Methylprednisolone

In animal studies, pre-operative and post-operative subcutaneous administration of methylprednisolone (0.35 mg/kg/three times a week) had a negative effect on bone-implant osseointegration in one study on rabbits (95). This study used screw-type titanium implants, and it showed that methylprednisolone impaired bone-implant contact and the total peri-implant bone area. However, combining this drug with zoledronic acid (7.5 μg/kg/once a week, IV) resulted in a better BIO in one study on rabbits (95).

3.4.5.6.4.2 Prednisolone

In animal studies, pre-operative and post-operative intramuscular administration of prednisolone (10 mg/kg/daily) did show a negative effect on bone-implant osseointegration in the mandible but did not show any significant effect on bone-implant osseointegration in the tibia in the same study on rabbits (265). This study used screw-type titanium implants. Bone to implant contact, bone density, and removal torque test analyses showed that prednisolone had no significant effect on bone-implant osseointegration in the mandible, but it did have a negative effect on the tibia.

3.4.5.6.4.3 Glucocorticosteroid

In animal studies, the use of glucocorticosteroids (different doses from 5-60 mg) was not associated with a high risk of implant failure in one retrospective cohort study on dental implants (266).

3.4.5.7 Chemotherapy

Different Chemotherapy drugs such as cisplatin, methotrexate, doxorubicin, ifosfamide have been assessed for their impact on bone-implant osseointegration.

In human studies, chemotherapy was associated with a higher risk of implant failure in one prospective cohort study (some combination of methotrexate, cyclophosphamide, doxorubicin, ifosfamide, cisplatin, etoposide, and various other agents) (267) while no effect on another prospective cohort study (cis- or carboplatin and 5-fluorouracil in three cycles) (268). This association was statistically significant in the first study, which included 24 non-users and 30 users of chemotherapy but was not in the other study that was done on 60 non-users and 30 users of chemotherapy. Underneath we discuss the literature on specific types of chemotherapy drugs.

3.4.5.7.1 Cisplatin

In animal studies, pre-operative and post-operative systemic administration of cisplatin (50, 75, 150 mg/m^2/once a week) had a negative effect on bone-implant osseointegration in two studies on dogs and one study on rabbits (269-271). Two of these studies used porous-surface titanium implants and the other one used screw-type titanium dental implants. Bone-to-implant contact, bone ingrowth analyses, and torque force tests showed that cisplatin impaired bone-implant osseointegration.

3.4.5.7.2 Methotrexate

In animal studies, pre-operative intramuscular administration of low dose methotrexate (3 mg/kg/once a week) had no negative effect on bone-implant osseointegration in one study on rabbits (272). This study used screw-shaped titanium implants, and it showed that methotrexate did not impair bone-to-implant contact and the total peri-implant bone area.

3.4.5.7.3 Doxorubicin

In animal studies, pre-operative and post-operative systemic administration of doxorubicin (20 mg/m^2/once a week) had a negative effect on bone-implant osseointegration in one study on dogs (271). This study used porous-surface titanium implants. Bone-to-implant contact, bone ingrowth analyses, and torque force tests showed that doxorubicin impaired bone-implant osseointegration.

3.4.5.7.4 Ifosfamide

In animal studies, pre-operative and post-operative systemic administration of ifosfamide (300 mg/m^2/once a week) had a negative effect on bone-implant osseointegration in one study on dogs (271). This study used porous-surface titanium implants. Bone-to-implant contact, bone ingrowth, and torque force analyses showed that ifosfamide impaired bone-implant osseointegration.

3.4.5.8 Anti-Angiogenic

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

3.4.5.8.1 TNP-470

In animal studies, post-operative subcutaneous administration of TNP-470 (10 mg/kg/three days a week) was found to have a negative effect on osseointegration in one study on rabbits (273). This study used screw-shaped titanium implants, and it showed that TNP-470 impaired bone-to-implant contact and new bone formation around the implants.

3.4.5.8.2 Anti-vascular endothelial growth factor (Anti-VEGF)

In animal studies, post-operative intraperitoneal administration of anti-VEGF (4 μg/kg) was found to have a negative effect on osseointegration in one study on rats (274). This study used

cylindrical titanium implants, and it showed that anti-VEGF impaired bone-to-implant contact and peri-implant bone formation.

3.4.5.8.3 Ranibizumab

In animal studies, post-operative intraperitoneal administration of ranibizumab (15 μg/kg) was found to have a negative effect on osseointegration in one study on rats (274). This study used cylindrical titanium implants, and it showed that ranibizumab impaired bone-to-implant contact and peri-implant bone formation.

3.4.5.9 Antibiotic

Different antibiotics such as amoxicillin and doxycycline have been assessed for their impact on bone-implant osseointegration.

In human studies, pre-operative administration of antibiotics prior to implant placement had no significant effect on implant failure in 3 randomized controlled clinical trials (275-277) and one retrospective cohort study (278).

In animal studies, one study on rats showed that amoxicillin had a negative effect on osseointegration when used at a pre-operative dose of 40mg/kg and a post-operative dose of 10 mg/kg at day 3, 5, and 7 (279). On the other hand, postoperative oral administration of doxycycline (16.67 mg/kg) showed a positive effect on the bone-to-implant contact in diabetic rats (280).

3.4.5.10 Anti-Diabetic

Three drugs commonly used for diabetes, such as insulin, aminoguanidine, and metformin have been assessed for their impact on bone-implant osseointegration. Underneath we discuss the literature on the specific types of anti-diabetic drugs.

3.4.5.10.1 Insulin

In animal studies, different doses of insulin have been assessed for their impact on bone-implant osseointegration. Insulin doses of 2-17 IU/day were found to have a positive effect on osseointegration in seven different studies on diabetic rats (198, 281-286). Three of these studies used screw-form implants, two used cylindrical implants, one used the rod-shaped implants, and one used dental titanium implants. These studies showed that insulin improved bone-to-implant contact and the bone area within the limits of the implant threads. On the other hand, one study on diabetic rabbits using dose 20 IU/day did not show any significant effect (287). This study used unthreaded titanium implants, and it showed that insulin did not affect the bone-implant contact during the removal torque test. Also, combining insulin with vitamin D (12 μg/kg/daily, gavage) resulted in improved BIO in one study on diabetic rats (198).

3.4.5.10.2 Metformin

In animal studies, 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 have a positive effect on osseointegration in two of these studies (288, 289), while long term use of oral metformin (40 mg/kg/daily) showed a negative effect on osseointegration in the third study (289). 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.

3.4.5.10.3 Aminoguanidine

In animal studies, different doses of aminoguanidine have been assessed for their impact on bone-implant osseointegration in two studies on rats. Intraperitoneally administration of aminoguanidine (10-132.2 mg/kg/daily) was found to have a positive effect on osseointegration in both studies (280, 290). One study used screw-form titanium implants, and the other used cylindrical titanium implants. These studies showed that aminoguanidine improved bone-to-implant contact, bone marrow to implant contact, and the results of the counter-torque test.

3.4.5.11 Cardiovascular System Drugs

3.4.5.11.1 Antihypertensive

In human studies, systemic administration of antihypertensive medications was associated with an increase in the survival rate of osseointegrated implants in one retrospective cohort study (291). Also, different hypertension drugs such as propranolol and nifedipine have been assessed in vivo for their impact on bone-implant osseointegration.

3.4.5.11.1.1 Propranolol

In animal studies, post-operative subcutaneous administration of propranolol (5 mg/kg/daily) was found to have a positive effect on osseointegration in one study on rats (292). This study used cylindrical titanium implants, and it showed that propranolol improved bone-to-implant contact.

3.4.5.11.1.2 Nifedipine

In animal studies, post-operative subcutaneous administration of nifedipine (50 mg/kg/daily) in combination with the immunosuppressive drug CsA (10 mg/kg/daily) was found to have no

significant effect on osseointegration in one study on rabbits (293). This study used screw-shaped titanium implants, and it showed that the administration of nifedipine in combination with the immunosuppression drug for a short period of time had no significant effects on peri-implant bone density.

3.4.5.11.2 Statins

In human studies, use of statins was significantly associated with an increased survival rate of osseointegrated implants at 5 years in a retrospective cohort study on total hip arthroplasty (294).

In animal studies, post-operative subcutaneous, intraperitoneal, and oral administration of simvastatin (3-10 or 25-50 mg/kg) was found to have a positive effect on osseointegration in eight animal studies (295) (188, 189, 296-300). Three of these 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 (2 screw-shaped, 2 unspecified implant design, 2 hydroxyapatite-coated, 1 cylindrical-shaped), and one used grit-blasted implants. Bone-to-implant contact, the bone area within the limits of implant threads, peri-implant bone quality, and bone density, and push-out test analyses showed that simvastatin enhanced bone-implant osseointegration. 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) had a positive effect on bone-implant osseointegration (188, 189). 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 in one study on rats (301). This study used HA-coated stainless-steel implants in which bone-to-implant contact and peri-implant bone density analysis showed that simvastatin had no effect on bone-implant osseointegration.

3.4.5.12 Blood Drugs

3.4.5.12.1 Anti-Hemorrhagic: Aprotinin

In animal studies, post-operative intravenous administration of aprotinin (7,200 KIU) was found to have no effect on osseointegration in one study on rats (302). This study used steel Kirschner-wires. Bone-to-implant contact and push-out force analyses showed that systemic administration of aprotinin had no effect on BIO.

3.4.5.12.2 Anti-Thrombotic: Warfarin

In animal studies, post-operative oral administration of warfarin (5 mg/kg) was found to have a negative effect on osseointegration in one study on goats (303). This study used cylindrical hydroxyapatite-coated cobalt-chromium-molybdenum alloy implants. Bone-to-implant contact and push-out force analyses showed that systemic administration of warfarin impaired BIO. However, hydroxyapatite-coated reverse the negative effect and improve BIO.

3.4.5.13 Immunosuppression

Different immunosuppressive medications such as cyclosporin A and FK-506 have been assessed for their impact on bone-implant osseointegration.

3.4.5.13.1 Cyclosporin A

In animal studies, pre-operative and post-operative subcutaneous administration of cyclosporin A (10 mg/kg/daily) was found to have a negative effect on osseointegration in five studies on rabbits (304-308). 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 in one study on rats (309). This study used a threaded titanium cylindrical chamber. Bone-to-implant contact and peri-implant bone area analyses showed that a low dose of cyclosporin A had no effect on bone-implant osseointegration. Moreover, Post-operative subcutaneous administration of cyclosporin A (10 mg/kg, daily) in combination with nifedipine (50 mg/kg, daily) and antihypertension medications were found to have no effect on osseointegration in one study on rabbits (293).

3.4.5.13.2 FK-506

In animal studies, pre-operative and post-operative subcutaneous administration of FK-506 (1 mg/kg) was found to have a negative effect on osseointegration in one study on rats (310). This study used sandblasted titanium implants, and it showed that FK-506 impaired bone-implant contact and peri-implant bone formation.

3.4.5.14 Anti-Gastric:

3.4.5.14.1 Proton Pump Inhibitors (PPI)

In human studies, systemic administration of Proton Pump Inhibitors (PPIs) was associated with a higher risk of implant failure in two retrospective cohort studies (311, 312).

In animal studies, post-operative intraperitoneal administration of Proton Pump Inhibitors (PPIs) (5 mg/kg/daily) was found to have a negative effect on osseointegration in one study on rats. This study used titanium implants, and it showed that Proton Pump Inhibitors (PPIs) impaired bone-implant contact and peri-implant bone formation (313).

3.4.5.15 Hyperbaric oxygen (HBO)

In animal studies, post-operative systemic administration of HBO treatment (10 sessions, 2.0-2.5 ATM of pure oxygen, 90 minutes/day) was found to have a positive effect on early healing of osseointegration in two studies on diabetic rabbits and diabetic rats (314, 315). One of these studies used screw dental implants, and the other used screw-shaped titanium implants, and they showed that HBO improved bone-implant osseointegration under diabetic conditions. On the other hand, one study on rats showed that of HBO treatment (10 sessions, 2.80 ATM of pure oxygen, 120 minutes/twice a day) had no effect on BIO in irradiated rats (316). This study used a screw-shaped titanium implant. Bone-to-implant contacts and removal torque test analyses showed that 10 sessions of HBO treatment had no effect on BIO in irradiated rats.

3.4.6 Synthesis of results

The qualitative synthesis summary of the collected data is shown in three critical analyses: RCT studies, observational studies, and animal studies.

Table 3: Number of articles identified per drug category as a function of screening method used to identify the study, the type of study, and the study outcome regarding the effect of the drug on osseointegration.

Drug classes identified	Number of studies identified per drug							
	Screening method		Study design and outcome					
	Manual screening of specific search strategies	AI screening of highly sensitive search strategy	Human			Animal		
			+ve	-ve	NS	+ve	-ve	NS
Nicotine (236-242) (243, 244)	6	9	0	0	0	0	4	5
Nicotine + PTH (191)	1	1	0	0	0	1	0	0
Nicotine + alcohol (241)	1	1	0	0	0	0	1	0
Antibiotic (275-280)	2	6	0	0	4	1	1	0
Strontium ranelate (76, 206-208)	4	4	0	0	0	4	0	0
NSAID (124, 209-228)	15	21	2	1	5	0	10	9
Melatonin (232)	1	1	0	0	0	1	0	0
Bisphosphonate (61-147, 149-170)	57	104	29	4	13	48	3	6
Raloxifene (132)	1	1	0	0	0	1	0	0
Chemotherapy (267-272)	5	6	0	1	1	0	5	1
Corticosteroids (95, 265, 266)	2	3	0	0	1	0	2	1
Corticosteroids + Bisphosphonate (92, 94, 95)	3	3	0	0	0	1	1	1
PTH (64, 87, 137, 160, 164-166, 171-197)	26	33	6	0	1	26	0	3
Anti-diabetic (198, 280-290)	4	12	0	0	0	11	1	1
Anti-diabetic + Vitamin D (198)	0	1	0	0	0	1	0	0
Alcohol (241, 245-248)	2	5	0	0	0	0	5	0
Antihypertensive (291-293)	2	3	1	0	0	1	0	1
Local anesthesia (231)	1	1	1	0	0	0	0	0
Thyroid hormone replacement (124, 133, 251, 252, 259-262)	4	8	2	0	0	5	1	0
Sex hormone replacement (134, 136, 169, 249-258)	9	12	1	0	1	9	0	1
Sex hormone replacement + Bisphosphonate (110)	0	1	0	0	0	1	0	0
Anti-RANKL (130, 205)	2	2	0	0	0	2	0	0
Anti-angiogenic (273, 274)	2	2	0	0	0	0	3	0
Immunosuppression (304-310)	5	7	0	0	0	0	6	1
Immunosuppression + nifedipine (293)	0	1	0	0	0	0	0	1
Statin (188, 189, 294-301)	6	10	1	0	0	8	0	1
Statin + PTH (188, 189)	2	2	0	0	0	2	0	0
Oxytocin (263, 264)	2	2	0	0	0	2	0	0
Vitamin D (101, 109, 131, 198-202)	4	8	0	0	2	5	1	0
Vitamin D + Bisphosphonate (131)	1	1	0	0	0	1	0	0
Antidepressant (234, 235)	2	2	0	2	0	0	0	0
Antipsychotic (233)	1	1	0	0	0	1	0	0
PPI (311-313)	3	3	0	2	0	0	1	0
Aprotinin (302)	1	1	0	0	0	0	0	1
Hyperbaric oxygen (314-316)	1	3	0	0	0	2	0	1
Warfarin (303)	1	1	0	0	0	0	1	0
Anti-Sclerostin antibody (203, 204)	0	2	0	0	0	2	0	0
Prostaglandin EP4 receptor agonist (229)(317)	0	2	0	0	0	2	0	0
Cannabis (230)	0	1	0	0	0	0	1	0

NS: a study showing no significant differences between control and drug-treated group; -ve: negative; +ve: positive

3.4.7 Discussion

This study achieved two key objectives, it provided a new 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 screen automatically 543927 articles by only having to screen manually 1.49 % of the total dataset. This allowed us to retrieve 268 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 mapping is scarce, and only two groups have done this. A study from Lam, J. et al., on the effect of low-calorie sweeteners (LCS) on health outcomes (5), and the tool of Tripdatabase.com for fully automated mapping (6). Our method required a lower percentage of manual article screening than Lam, J. et al. (1.49% vs. 28%), and even though Tripdatabase does not require manual screening, our method was able to detect far more relevant articles. The clinical search engine Tripdatabase.com includes an artificial intelligence (AI) for full automation of evidence mapping that does not require any manual screening by the user (6). However, this prototype can only perform automated evidence synthesis for RCT and SR, and it can't identify and synthesize observational or animal studies (6). In order to compare our systematic mapping with the performance of the 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 than 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 tool for evidence

mapping review, our algorithm for systematic mapping is the first that has been validated against published systematic reviews performed by humans (5, 6).

Our algorithm was validated against 2 already published systematic reviews (Chappuis et al.) (Aghaloo et al.) with search strategies that falls within the scope of ours (3) (318). 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 perhaps could have missed up to 7% of relevant clinical studies. Nevertheless, our review included 76 more clinical studies (five-folds) compared to Chappuis et al. article (3) including 28 RCTs compared to 2 articles identified by Chappuis et al., and 48 observational studies compared to 12 articles identified by Chappuis et al. (3). Also, we were able to identify 14 drug classes assessed in clinical studies compared to 5 drug classes identified by Chappuis et al. article (3). Upon validation with the systematic review of Aghaloo et al. (318), 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 processes. For instance, Warfarin, NSAID, and Aspirin are known to impair hemostasis, and they were found to have a negative effect on 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 (Table 4). These observations confirm our hypothesis stating that drugs affecting the pathways of bone healing have an effect on osseointegration (61-316).

Table 4: The stages of osseointegration that could be affected by the drugs identified in our review (61-316).

Stages of osseointegration	Drugs that could affect each stage
Hemostasis and Thrombosis	Warfarin, NSAID (Aspirin), and SSRIs
Inflammation	Cannabis, Immunosuppression, Corticosteroids, Antibiotics, Alcohol, Anti-diabetic, NSAID, and SSRIs.
Proliferation	Chemotherapy, Nicotine, Alcohol, Corticosteroids, Cannabis, Hyperbaric oxygen, Aprotinin, Melatonin, Anti-angiogenic, PTH, and Antibiotics.
Remodeling	Chemotherapy, Corticosteroids, Antibiotics, Prostaglandin EP4 receptor agonist, Anti-Sclerostin antibody, Statin, PPI, Lithium chloride, SSRIs, Vit D, Oxytocin, Anti-RANKL, Estradiol, Dihydrotestosterone, Thyroid hormone replacement, Strontium ranelate, Bisphosphonate Antihypertensive, Glucocorticoids, Anti-diabetic, PTH, Raloxifene, and Melatonin.

Differences between orthopaedic and Craniofacial osseointegration

Craniofacial bone and skeletal bone have different embryological origins and metabolism. Thus, drugs and osseointegrated implants could behave differently in these two types of bone. Among the 12 drugs and drug categories assessed for their effect on implant osseointegration in both craniofacial and skeletal bones, most were found to have similar effects on both types of bone. This included Zoledronic Acid, Alendronate, Ibuprofen, 17β estradiol, Alcohol, Anti-Hypertensive, and PTH (Table 5, and Figure 13). However, Diclofenac sodium, Prednisolone, Amoxicillin and Chemotherapy had a negative effect on osseointegration of orthopedic implants

(213, 214, 265, 267), but did not show a significant effect on craniofacial implants (215, 216, 265, 268) (275-279). On the other hand, metformin was found to have a positive effect on orthopedic implants (288), while having a negative effect on craniofacial implants, (Table 5, and Figure 13) (289).

Craniofacial implants;

Few drugs were assessed only in craniofacial bone but not in skeletal bones. These include SSRI, PPI, Glucocorticosteroids, Non-specific NSAID, Parecoxib, Flurbiprofen, and Bupivacaine without vasoconstrictor (Table 5, and Figure 13). On the other hand, a large number of drugs were assessed on implants placed on skeletal bones but not in craniofacial 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, Xianlinggubao, 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, and Cannabis (Table 5 and Figure 13).

Future research should be performed to assess the effect of these drugs on both craniofacial and skeletal bones.

Table 5: The list of the drugs that were tested in each type of bone.

Type of bone	Drugs that could affect each type of bone
Orthopaedic	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, Xianlinggubao, 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, and Cannabis
Craniofacial	SSRI, PPI, Glucocorticosteroids, Non-specific NSAID, Parecoxib, Flurbiprofen, and Bupivacaine without vasoconstrictor.
Orthopaedic and Craniofacial	Zoledronic Acid, Alendronate, Ibuprofen, 17β estradiol, Alcohol, Anti-Hypertensive, PTH, Diclofenac sodium, Prednisolone, Amoxicillin and Chemotherapy, and Metformin.

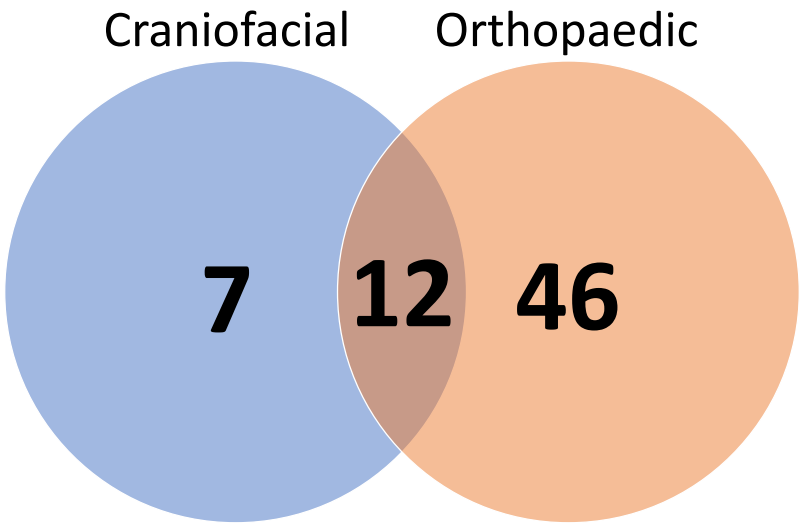

Figure 13: Venn diagram showing the number of drugs that were tested in each type of bone.

3.4.8 Limitations, Strength and future work

The main limitation of this study is that we searched only the Pubmed database because of its unique high-quality MeSH-terms, and thus we may have lost some publications found in other databases. Also, the Pubmed database has a delay in publishing the MeSH-terms of each article, thus some recently published studies might have been missed by our search method. Nevertheless, focusing on the Pubmed database, and the use of MeSH-terms allowed us to achieve excellent results. Another limitation of our algorithm was that 5% of the articles included were false-positives, and 7% were false-negatives; thus, manual screening is still mandatory to identify such

articles. Therefore, new methods are required to reduce manual screening of false-positive articles and to reduce the false-negative rate.

Also, our results in this thesis, guide researchers towards identifying the research gaps related to the effect of pharmacological agents on osseointegration and could help suggest future clinical studies on the effect of pharmacological drugs on implant osseointegration.

3.4.9 Conclusions

MeSH-term classifier trained with a dataset that includes non-similar studies only requires manual screening of 1.49% of the original search of an evidence mapping review. This approach could make complex systematic reviews or evidence mapping reviews increasingly time-efficient and allows us to answer a complex question such as, "What drugs could affect bone-implant osseointegration?". Our evidence mapping on this specific subject revealed that drugs known to affect the metabolic activities involved in the process of osseointegration could indeed affect osseointegration.

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Appendices

Appendix A: Search Strategies

Table 6: Search Strategies used for the systematic mapping

Type of search	Mesh terms and keywords
A. Specific search strategy for similar articles	
	"Osseointegration/drug effects"[MeSH Terms]
B. Specific search strategy for non-similar articles	
	("Dental Implants"[Mesh]) AND ("14-alpha Demethylase Inhibitors" OR ("5-alpha+Reductase+Inhibitors") OR ("5-Lipoxygenase-Activating+Protein+Inhibitors") OR

	("Abortifacient+Agents"") OR ("Abortifacient+Agents") OR (""Abortifacient+Agents") OR ("Acaricides" ") OR ("Acetaldehyde+Dehydrogenase+Inhibitors") OR ("Acetylcholine+Release+Inhibitors") OR ("Acid+Sensing+Ion+Channel+Blockers") OR ("Adenosine+A1+Receptor+Agonists") OR ("Adenosine+A1+Receptor+Antagonists") OR ("Adenosine+A2+Receptor+Agonists") OR ("Adenosine+A2+Receptor+Antagonists") OR ("Adenosine+A3+Receptor+Agonists") OR ("Adenosine+A3+Receptor+Antagonists") OR ("Adenosine+Deaminase+Inhibitors") OR ("Adenylyl+Cyclase+Inhibitors") OR ("Adhesives") OR (""Adjuvants") OR ("Adjuvants") OR (""Adjuvants") OR ("Adrenal+Cortex+Hormones") OR ("Adrenergic+Agents") OR ("Adrenergic+Agonists") OR ("Adrenergic+alpha-1+Receptor+Agonists") OR ("Adrenergic+alpha-1+Receptor+Antagonists") OR ("Adrenergic+alpha-2+Receptor+Agonists") OR ("Adrenergic+alpha-2+Receptor+Antagonists") OR ("Adrenergic+alpha-Agonists") OR ("Adrenergic+alpha-Antagonists") OR ("Adrenergic+Antagonists") OR ("Adrenergic+beta-1+Receptor+Agonists") OR ("Adrenergic+beta-1+Receptor+Antagonists") OR ("Adrenergic+beta-2+Receptor+Agonists") OR ("Adrenergic+beta-2+Receptor+Antagonists") OR ("Adrenergic+beta-3+Receptor+Agonists") OR ("Adrenergic+beta-3+Receptor+Antagonists") OR ("Adrenergic+beta-Agonists") OR ("Adrenergic+beta-Antagonists") OR ("Adrenergic+Uptake+Inhibitors") OR ("Aerosol+Propellants") OR ("Affinity+Labels") OR ("Agglutinins") OR ("Air+Pollutants") OR ("Air+Pollutants") OR ("Air+Pollutants") OR ("Alarmins") OR ("Alcohol+Deterrents") OR ("Alkylating+Agents") OR ("Amebicides") OR ("Amylin+Receptor+Agonists") OR ("Anabolic+Agents") OR ("Analgesics") OR ("Analgesics") OR ("Analgesics") OR ("Androgen+Antagonists") OR ("Androgen+Receptor+Antagonists") OR ("Androgens") OR ("Anesthetics") OR ("Anesthetics") OR ("Anesthetics") OR ("Anesthetics") OR ("Anesthetics") OR ("Anesthetics") OR ("Anesthetics") OR ("Angiogenesis+Inducing+Agents") OR ("Angiogenesis+Inhibitors") OR ("Angiogenesis+Modulating+Agents") OR ("Angiotensin-Converting+Enzyme+Inhibitors") OR ("Angiotensin+II+Type+1+Receptor+Blockers") OR ("Angiotensin+II+Type+2+Receptor+Blockers") OR ("Angiotensin+Receptor+Antagonists") OR ("Anion+Exchange+Resins") OR ("Antacids") OR ("Anthelmintics") OR ("Anti-Allergic+Agents") OR ("Anti-Anxiety+Agents") OR ("Anti-Arrhythmia+Agents") OR ("Anti-Asthmatic+Agents") OR ("Anti-

	Bacterial+Agents") OR ("Anti-Dyskinesia+Agents") OR ("Anti-HIV+Agents") OR ("Anti-Infective+Agents") OR ("Anti-Infective+Agents") OR ("Anti-Infective+Agents") OR ("Anti-Inflammatory+Agents") OR ("Anti-Inflammatory+Agents") OR ("Anti-Obesity+Agents") OR ("Anti-Retroviral+Agents") OR ("Anti-Ulcer+Agents") OR ("Antibiotics") OR ("Antibiotics") OR ("Anticarcinogenic+Agents") OR ("Anticestodal+Agents") OR ("Anticholesteremic+Agents") OR ("Anticoagulants") OR ("Anticonvulsants") OR ("Antidepressive+Agents") OR ("Antidepressive+Agents") OR ("Antidepressive+Agents") OR ("Antidiarrheals") OR ("Antidiuretic+Agents") OR ("Antidiuretic+Hormone+Receptor+Antagonists") OR ("Antidotes") OR ("Antiemetics" ("Antifibrinolytic+Agents") OR ("Antifoaming+Agents") OR ("Antifungal+Agents") OR ("Antihypertensive+Agents") OR ("Antimalarials") OR ("Antimanic+Agents") OR ("Antimetabolites") OR ("Antimetabolites") OR ("Antimitotic+Agents") OR ("Antimutagenic+Agents") OR ("Antinematodal+Agents") OR ("Antineoplastic+Agents") OR ("Antineoplastic+Agents") OR ("Antineoplastic+Agents") OR ("Antineoplastic+Agents") OR ("Antineoplastic+Agents") OR ("Antioxidants") OR ("Antiparasitic+Agents") OR ("Antiparkinson+Agents") OR ("Antiperspirants") OR ("Antiplatyhelmintic+Agents") OR ("Antiprotozoal+Agents") OR ("Antipruritics") OR ("Antipsychotic+Agents") OR ("Antipyretics") OR ("Antirheumatic+Agents") OR ("Antisickling+Agents") OR ("Antispermatogenic+Agents") OR ("Antithrombins") OR ("Antithyroid+Agents") OR ("Antitreponemal+Agents") OR ("Antitrichomonal+Agents") OR ("Antitubercular+Agents") OR ("Antitussive+Agents") OR ("Antiviral+Agents") OR ("Appetite+Depressants") OR ("Appetite+Stimulants") OR ("Aromatase+Inhibitors") OR ("Aromatic+Amino+Acid+Decarboxylase+Inhibitors") OR ("Astringents") OR ("Autonomic+Agents") OR ("Aversive+Agents") OR ("beta-Lactamase+Inhibitors") OR ("Biocompatible+Materials") OR ("Bleaching+Agents") OR ("Blood+Substitutes") OR ("Bone+Cements") OR ("Bone+Density+Conservation+Agents") OR ("Bradykinin+B1+Receptor+Antagonists") OR ("Bradykinin+B2+Receptor+Antagonists") OR ("Bradykinin+Receptor+Antagonists") OR ("Bronchoconstrictor+Agents") OR ("Bronchodilator+Agents") OR ("Buffers") OR ("Calcimimetic+Agents") OR ("Calcineurin+Inhibitors") OR ("Calcium+Channel+Agonists") OR

	("Calcium+Channel+Blockers") OR ("Calcium+Chelating+Agents") OR ("Calcium+Ionophores") OR ("Cannabinoid+Receptor+Agonists") OR ("Cannabinoid+Receptor+Antagonists") OR ("Cannabinoid+Receptor+Modulators") OR ("Carbonic+Anhydrase+Inhibitors") OR ("Carcinogens") OR ("Carcinogens") OR ("Cardiotonic+Agents") OR ("Cardiovascular+Agents") OR ("Cariogenic+Agents") OR ("Cariostatic+Agents") OR ("Caspase+Inhibitors") OR ("Catechol+O-Methyltransferase+Inhibitors") OR ("Cathartics") OR ("Cation+Exchange+Resins") OR ("Caustics") OR ("CCR5+Receptor+Antagonists") OR ("Central+Nervous+System+Agents") OR ("Central+Nervous+System+Depressants") OR ("Central+Nervous+System+Stimulants") OR ("Chelating+Agents") OR ("Chemical+Warfare+Agents") OR ("Chemosterilants") OR ("Chloride+Channel+Agonists") OR ("Cholagogues+and+Choleretics") OR ("Cholinergic+Agents") OR ("Cholinergic+Agonists") OR ("Cholinergic+Antagonists") OR ("Cholinesterase+Inhibitors") OR ("Cholinesterase+Reactivators") OR ("Chromogenic+Compounds") OR ("Coagulants") OR ("Coccidiostats") OR ("Colloids") OR ("Coloring+Agents") OR ("Complement+Inactivating+Agents") OR ("Contraceptive+Agents") OR ("Contraceptive+Agents") OR ("Contraceptive+Agents") OR ("Contraceptives") OR ("Contraceptives") OR ("Contraceptives") OR ("Contraceptives") OR ("Contraceptives") OR ("Contraceptives") OR ("Contraceptives") OR ("Contraceptives") OR ("Contrast+Media") OR ("Convulsants") OR ("Cosmetics") OR ("Cross-Linking+Reagents") OR ("Cryoprotective+Agents") OR ("Culture+Media") OR ("Cyclooxygenase+2+Inhibitors") OR ("Cyclooxygenase+Inhibitors") OR ("Cysteine+Proteinase+Inhibitors") OR ("Cystine+Depleting+Agents") OR ("Cytochrome+P-450+CYP1A2+Inducers") OR ("Cytochrome+P-450+CYP1A2+Inhibitors") OR ("Cytochrome+P-450+CYP2B6+Inducers") OR ("Cytochrome+P-450+CYP2B6+Inhibitors") OR ("Cytochrome+P-450+CYP2C19+Inducers") OR ("Cytochrome+P-450+CYP2C19+Inhibitors") OR ("Cytochrome+P-450+CYP2C8+Inducers") OR ("Cytochrome+P-450+CYP2C8+Inhibitors") OR ("Cytochrome+P-450+CYP2C9+Inducers") OR ("Cytochrome+P-450+CYP2C9+Inhibitors") OR ("Cytochrome+P-450+CYP2D6+Inhibitors") OR ("Cytochrome+P-450+CYP2E1+Inhibitors") OR ("Cytochrome+P-450+CYP3A+Inducers") OR ("Cytochrome+P-450+CYP3A+Inhibitors") OR ("Cytochrome+P-450+Enzyme+Inhibitors") OR ("Cytostatic+Agents") OR ("Cytotoxins") OR ("Defoliants") OR ("Delayed-Action+Preparations") OR

	("Dental+Disinfectants") OR ("Dental+Materials") OR ("Dentifrices") OR ("Dermatologic+Agents") OR ("Dermotoxins") OR ("Detergents") OR ("Diagnostic+Uses+of+Chemicals") OR ("Dialysis+Solutions") OR ("Dipeptidyl-Peptidase+IV+Inhibitors") OR ("Disinfectants") OR ("Diuretics") OR ("Diuretics") OR ("Dopamine+Agents") OR ("Dopamine+Agonists") OR ("Dopamine+Antagonists") OR ("Dopamine+D2+Receptor+Antagonists") OR ("Dopamine+Uptake+Inhibitors") OR ("Drug+Carriers") OR ("Emetics") OR ("Emollients") OR ("Endocrine+Disruptors") OR ("Endothelin+A+Receptor+Antagonists") OR ("Endothelin+B+Receptor+Antagonists") OR ("Endothelin+Receptor+Antagonists") OR ("Endothelium-Dependent+Relaxing+Factors") OR ("Environmental+Pollutants") OR ("Enzyme+Activators") OR ("Enzyme+Inhibitors") OR ("Enzyme+Reactivators") OR ("Epithelial+Sodium+Channel+Blockers") OR ("Estrogen+Antagonists") OR ("Estrogen+Receptor+Antagonists") OR ("Estrogen+Receptor+Modulators") OR ("Estrogens") OR ("Estrogens") OR ("Excipients") OR ("Excitatory+Amino+Acid+Agents") OR ("Excitatory+Amino+Acid+Agonists") OR ("Excitatory+Amino+Acid+Antagonists") OR ("Expectorants") OR ("Explosive+Agents") OR ("Factor+Xa+Inhibitors") OR ("Fat+Emulsions") OR ("Fat+Substitutes") OR ("Fatty+Acid+Synthesis+Inhibitors") OR ("Fertility+Agents") OR ("Fertility+Agents") OR ("Fertility+Agents") OR ("Fertilizers") OR ("Fibrin+Modulating+Agents") OR ("Fibrinolytic+Agents") OR ("Filaricides") OR ("Fixatives") OR ("Flame+Retardants") OR ("Flavoring+Agents") OR ("Fluorescent+Dyes") OR ("Folic+Acid+Antagonists") OR ("Food+Additives") OR ("Food+Coloring+Agents") OR ("Food+Preservatives") OR ("Free+Radical+Scavengers") OR ("Fungicides") OR ("GABA-A+Receptor+Agonists") OR ("GABA-A+Receptor+Antagonists") OR ("GABA+Agents") OR ("GABA+Agonists") OR ("GABA+Antagonists") OR ("GABA-B+Receptor+Agonists") OR ("GABA-B+Receptor+Antagonists") OR ("GABA+Modulators") OR ("GABA+Uptake+Inhibitors") OR ("Ganglionic+Blockers") OR ("Ganglionic+Stimulants") OR ("Gasotransmitters") OR ("Gastrointestinal+Agents") OR ("Glucocorticoids") OR ("Glycine+Agents") OR ("Glycoside+Hydrolase+Inhibitors") OR ("Gout+Suppressants") OR ("Growth+Inhibitors") OR ("Growth+Substances") OR ("GTP+Phosphohydrolase+Activators") OR ("Guanylyl+Cyclase+C+Agonists") OR ("Hallucinogens") OR ("Hazardous+Substances") OR

	("Hemagglutinins") OR ("Hematinics") OR ("Hematologic+Agents") OR ("Hemolytic+Agents") OR ("Hemostatics") OR ("Heparin+Antagonists") OR ("Herbicides") OR ("Histamine+Agents") OR ("Histamine+Agonists") OR ("Histamine+Antagonists") OR ("Histamine+H1+Antagonists") OR ("Histamine+H1+Antagonists") OR ("Histamine+H2+Antagonists") OR ("Histamine+H3+Antagonists") OR ("Histone+Deacetylase+Inhibitors") OR ("HIV+Fusion+Inhibitors") OR ("HIV+Integrase+Inhibitors") OR ("HIV+Protease+Inhibitors") OR ("Hormone+Antagonists") OR ("Hormones") OR ("Hormones") OR ("Hydroxymethylglutaryl-CoA+Reductase+Inhibitors") OR ("Hygroscopic+Agents") OR ("Hypnotics+and+Sedatives") OR ("Hypoglycemic+Agents") OR ("Hypolipidemic+Agents") OR ("Immunologic+Factors") OR ("Immunosuppressive+Agents") OR ("Immunotoxins") OR ("Incretins") OR ("Indicators+and+Reagents") OR ("Insect+Repellents") OR ("Insecticides") OR ("Insulin+Antagonists") OR ("Intercalating+Agents") OR ("Interferon+Inducers") OR ("Ion+Exchange+Resins") OR ("Ionophores") OR ("Iron+Chelating+Agents") OR ("Irritants") OR ("Keratolytic+Agents") OR ("Laxatives") OR ("Leprostatic+Agents") OR ("Leukotriene+Antagonists") OR ("Lipid+Regulating+Agents") OR ("Lipoprotein+Lipase+Activators") OR ("Liposomes") OR ("Lipotropic+Agents") OR ("Lipoxygenase+Inhibitors") OR ("Lubricants") OR ("Luminescent+Agents") OR ("Luteolytic+Agents") OR ("Matrix+Metalloproteinase+Inhibitors") OR ("Membrane+Transport+Modulators") OR ("Menstruation-Inducing+Agents") OR ("Metabolic+Side+Effects+of+Drugs+and+Substances") OR ("Micronutrients") OR ("Mineralocorticoid+Receptor+Antagonists") OR ("Mineralocorticoids") OR ("Miotics") OR ("Mitogens") OR ("Mitosis+Modulators") OR ("Molecular+Probes") OR ("Molluscacides") OR ("Monoamine+Oxidase+Inhibitors") OR ("Mouthwashes") OR ("Muscarinic+Agonists") OR ("Muscarinic+Antagonists") OR ("Muscle+Relaxants") OR ("Mutagens") OR ("Mydriatics") OR ("Myeloablative+Agonists") OR ("Narcotic+Antagonists") OR ("Narcotics") OR ("Nasal+Decongestants") OR ("Natriuretic+Agents") OR ("Neurokinin-1+Receptor+Antagonists") OR ("Neuromuscular+Agents") OR ("Neuromuscular+Blocking+Agents") OR ("Neuromuscular+Depolarizing+Agents") OR ("Neuromuscular+Nondepolarizing+Agents") OR ("Neuroprotective+Agents") OR ("Neurotoxins") OR ("Neurotransmitter+Agents") OR ("Neurotransmitter+Uptake+Inhibitors") OR ("Nicotinic+Agonists") OR ("Nicotinic+Antagonists") OR

	("Nitric+Oxide+Donors") OR ("Nootropic+Agents") OR ("Noxae") OR ("Nucleic+Acid+Synthesis+Inhibitors") OR ("Ointment+Bases") OR ("Oligodeoxyribonucleotides") OR ("Oligonucleotides") OR ("Ophthalmic+Solutions") OR ("Orexin+Receptor+Antagonists") OR ("Ornithine+Decarboxylase+Inhibitors") OR ("Oxidants") OR ("Oxidants") OR ("Oxytocics") OR ("Parasympatholytics") OR ("Parasympathomimetics") OR ("Parenteral+Nutrition+Solutions") OR ("Perfume") OR ("Peripheral+Nervous+System+Agents") OR ("Peroxisome+Proliferators") OR ("Pesticide+Synergists") OR ("Pesticides") OR ("Pharmaceutic+Aids") OR ("Pharmaceutical+Solutions") OR ("Pharmaceutical+Vehicles") OR ("Phosphodiesterase+3+Inhibitors") OR ("Phosphodiesterase+4+Inhibitors") OR ("Phosphodiesterase+5+Inhibitors") OR ("Phosphodiesterase+Inhibitors") OR ("Phospholipase+A2+Inhibitors") OR ("Photoaffinity+Labels") OR ("Photosensitizing+Agents") OR ("Phytoestrogens") OR ("Plant+Growth+Regulators" ("Plasma+Substitutes") OR ("Plasticizers") OR ("Platelet+Aggregation+Inhibitors") OR ("Poisons") OR ("Poly(ADP-ribose)+Polymerase+Inhibitors") OR ("Potassium+Channel+Blockers") OR ("Potassium+Ionophores") OR ("Preservatives") OR ("Progestins") OR ("Prolyl-Hydroxylase+Inhibitors") OR ("Prostaglandin+Antagonists") OR ("Protease+Inhibitors") OR ("Proteasome+Inhibitors") OR ("Protective+Agents") OR ("Protein+Kinase+Inhibitors") OR ("Protein+Synthesis+Inhibitors") OR ("Proton+Ionophores") OR ("Proton+Pump+Inhibitors") OR ("Provitamins") OR ("Psychotropic+Drugs") OR ("Pulmonary+Surfactants") OR ("Purinergic+Agents") OR ("Purinergic+Agonists") OR ("Purinergic+Antagonists") OR ("Purinergic+P1+Receptor+Agonists") OR ("Purinergic+P1+Receptor+Antagonists") OR ("Purinergic+P2+Receptor+Agonists") OR ("Purinergic+P2+Receptor+Antagonists") OR ("Purinergic+P2X+Receptor+Antagonists") OR ("Purinergic+P2Y+Receptor+Antagonists") OR ("Pyrogens") OR ("Radiation-Protective+Agents") OR ("Radiation-Sensitizing+Agents") OR ("Radioactive+Pollutants") OR ("Radiopharmaceuticals") OR ("Reducing+Agents") OR ("Renal+Agents") OR ("Reproductive+Control+Agents") OR ("Resins") OR ("Respiratory+System+Agents") OR ("Reverse+Transcriptase+Inhibitors") OR ("Riot+Control+Agents") OR ("Rodenticides") OR ("Schistosomicides") OR ("Sclerosing+Solutions") OR ("Selective+Estrogen+Receptor+Modulators") OR ("Sensory+System+Agents") OR ("Sequestering+Agents") OR ("Serine+Proteinase+Inhibitors") OR ("Serotonin+5-

	HT1+Receptor+Agonists") OR ("Serotonin+5-HT1+Receptor+Antagonists") OR ("Serotonin+5-HT2+Receptor+Agonists") OR ("Serotonin+5-HT2+Receptor+Antagonists") OR ("Serotonin+5-HT3+Receptor+Agonists") OR ("Serotonin+5-HT3+Receptor+Antagonists") OR ("Serotonin+5-HT4+Receptor+Agonists") OR ("Serotonin+5-HT4+Receptor+Antagonists") OR ("Serotonin+Agents") OR ("Serotonin+and+Noradrenaline+Reuptake+Inhibitors") OR ("Serotonin+Antagonists") OR ("Serotonin+Receptor+Agonists") OR ("Serotonin+Uptake+Inhibitors") OR ("Siderophores") OR ("Sleep+Aids") OR ("Sodium+Channel+Agonists") OR ("Sodium+Channel+Blockers") OR ("Sodium+Chloride+Symporter+Inhibitors") OR ("Sodium+Ionophores") OR ("Sodium+Potassium+Chloride+Symporter+Inhibitors") OR ("Soil+Pollutants") OR ("Solvents") OR ("Spermatocidal+Agents") OR ("Steroid+Synthesis+Inhibitors") OR ("Sulfhydryl+Reagents") OR ("Sunscreening+Agents") OR ("Surface-Active+Agents") OR ("Surgical+Fixation+Devices") OR ("Sweetening+Agents") OR ("Sympatholytics") OR ("Sympathomimetics") OR ("Tear+Gases") OR ("Teratogens") OR ("Tissue+Adhesives") OR ("Tocolytic+Agents") OR ("Tooth+Bleaching+Agents") OR ("Topoisomerase+I+Inhibitors") OR ("Topoisomerase+II+Inhibitors") OR ("Topoisomerase+Inhibitors") OR ("Trace+Elements") OR ("Tranquilizing+Agents") OR ("Trypanocidal+Agents") OR ("Trypsin+Inhibitors") OR ("Tubulin+Modulators") OR ("Uncoupling+Agents") OR ("Uricosuric+Agents") OR ("Urological+Agents") OR ("Vasoconstrictor+Agents") OR ("Vasodilator+Agents") OR ("Vasopeptidase+Inhibitors") OR ("Viscoelastic+Substances") OR ("Viscosupplements") OR ("Vitamin+B+Complex") OR ("Vitamins") OR ("Voltage-Gated+Sodium+Channel+Agonists") OR ("Voltage-Gated+Sodium+Channel+Blockers") OR ("Wakefulness-Promoting+Agents") OR ("Water+Pollutants")}
C. Senstivie Search strategy	
	("Dental Implantation, Endosseous"[Mesh] OR ("Dental Implants"[Mesh]) OR "Osseointegration"[Mesh]) OR "Periprosthetic Fractures"[Mesh] OR "Drug Implants"[Mesh] OR "Internal Fixators"[Mesh] OR "Hip Prosthesis"[Mesh] OR "Prostheses and Implants"[Mesh] OR "Implants, Experimental"[Mesh] OR "Bone Screws"[Mesh] OR "Prosthesis Implantation"[Mesh]

Appendix B: Studies Characteristics

Table 7: Included studies characteristics.

Year	First Author	Type of Study	Drug	Drug route	Drug Dose	Sample Size	Outcome	Location
2003	Shirota T. et al.	a	Parathyroid hormone	SC	30 µg/kg	72 rats	bic	Japan
2018	Palin L.P. et al.	a	Melatonin	Oral	5 mg/kg	18 rats	bic	Brazil
2015	Cai W.X. et al.	a	Diclofenac Parecoxib	Oral SC	2 mg/kg 1.5 mg/kg	18 rabbits	bic	China
2011	Aspenberg P. et al	a	Alendronate OPG-Fc	SC	20 µg/kg 200 µg/kg 10 mg/kg	56 rats	bic	Sweden
2012	Yaman F. et al.	a	Zoledronic acid	IV	0.1 mg/kg	28 rabbits	bic	Turkey
2007	Avedian R.S. et al.	pr	Combination of methotrexate, cyclophosphamide, doxorubicin, ifosfamide, cisplatin, etoposide, and various other agents	NR	NR	54 patients	is	USA
2015	Rybaczek T. et al.	ex	Insulin Parathyroid hormone	SC “	100 IU/mL 60 mg/kg.	40 rats	bic	Austria
2009	Kasai T. et al.	RE	Alendronate	Oral	NR	51 patients, 11 with bis and 40 non-bis	is	USA
2005	Balatsouka D. et al.	ex	Nicotine	SC	3 mg/kg	16 rabbits	bic	Denmark
2008	Pablos A.B. et al.	ex	Diclofenac sodium and Meloxicam	IM	Diclofenac sodium 1.07 mg/kg. Meloxicam 0.2 mg/kg.	30 rats	bic	Brazil
2014	Li J.P. et al.	ex	Zoledronic acid	SC	0.1 mg/kg	46 rats	bic	China

2001	Kovacs A.F. et al	re	cis- or carboplatin and 5-fluorouracil	IV	Carboplatin 300 mg/m2and Cisplatin 100 mg/m2) and for both of 5-fluorouracil (1 g/m2)	30 patients	is	Germany
2010	Li Y. et al.	ex	Strontium Ranelate	Oral	200 and 400 mg/kg	40 rats	bic	China
2005	Duarte P.M. et al.	ex	Alendronate and 17β estradiol	SC	Alendronate 5 mg/kg and 17β estradiol 20 µg/kg	87 rats	bic	Brazil
2015	Bernhardsson M. et al.	ex	OPG-Fc and Alendronate	SC	OPG-Fc 8 mg/kg and Alendronate 20, 200 µg/kg	42 rats	bic	Sweden
1999	FH Jr N. et al.	ex	Calcitonin	IM	2 UI/kg single daily doses	30 rabbits	bic	Brazil
1999	Fiorellini J.P. et al.	ex	Insulin	IM	nr	10 rats	bic	USA
2017	Petsinis V. et al.	re	Glucocorticosteroid (prednisolone or methylprednisolone)	Inhalation or local	5 and 60 mg of prednisolone	31 patients	is	Greece
2011	Prieto-Alhambra D. et al.	re	Alendronate, Etidronate, Ibandronate, and Risedronate	Oral, IV, or Local	nr	41995 patients	is	UK
2015	Verzola M.H. et al.	ex	Alendronate	SC	1 mg/kg	160 rats	bic	Brazil
2002	Goodman S. et al.	ex	Naproxen and Rofecoxib	Oral	110 mg/kg Naproxen and 12.5 mg/kg Rofecoxib	8 rabbits	bic	USA
2007	Mair B. et al.	ex	TNP-470	SC	10 mg/kg	12 rabbits	bic	Austria
2012	Memon S. et al.	re	Alendronate, Ibandronate, and Risedronate	oral	nr	200 patients	is	USA

2005	Lionberger D.R. and P.C. Noble	rct	Celecoxib	Oral	200 mg/kg	54 patients	is	USA
2009	Ribeiro F.V. et al.	ex	Meloxicam	SC	3 mg/kg	30 rats	bic	Brazil
2008	Grant B.T. et al.	re	Alendronate, Ibandronate, and Risedronate	Oral	nr	458 participants	is	USA
2008	Nakamura Y.	ex	Alendronate and calcitriol	SC	0.1 mg/kg alendronate and 0.1 mg/kg calcitriol	64 rats	bic	Japan
2015	Siebert T. et al.	pr	Zoledronic acid	IV	5 mg/kg	24 patient	is	Slovakia
2008	Corsini M.S. et al.	ex	PTH	SC	6 µg/kg	20 rabbits	bic	Brazil
2007	Fugazzotto P.A. et al.	re	Alendronate, and Risedronate	Oral	35 mg/kg Alendronate and 70 mg/kg Risedronate	61 patient	is	USA
2007	Duka M. et al.	rct	Bupivacaine with/without a vasoconstrictor	Local anesthesia	3.5 cm3 of 0.5% bupivacaine with a vasoconstrictor (adrenalin, 1: 200 000)	30 patients	is	Serbia
2013	Kim I. et al.	ex	Zoledronic acid and Dexamethasone	IV ZA and IM Dexamethasone	0.01 mg/kg ZA and 1 mg/kg Dexamethasone	24 rabbits	bic	South Korea
2014	Dikicier E. et al.	ex	Zoledronic acid	IV	0.04 mg/kg	36 rats	bic	Turkey
2015	Ramalho-Ferreira G. et al.	ex	Alendronate and Raloxifene	Oral	0.1 mg/kg Alendronate and ral 1.0 mg/kg Raloxifene	72 rats	bic	Brazil
2011	Daugaard H. et al	ex	PTH	SC	5 µg/kg	20 canines	bic	Denmark

2010	Maimoun L. et al	ex	Strontium ranelate	Oral	625 mg/kg	30 rats	bic	Switzerland
2017	Zheng X. et al.	ex	(FK-506) tacrolimus	SC	1 mg/kg	32 mice	bic	China
2013	Almagro M.I. et al.	ex	PTH	SC	10 µg/kg	38 rabbits	bic	Spain
2016	Wu X. et al.	re	Hypertensive drugs	NR	nr	728 patients	is	Canada
2010	Yildiz A. et al.	ex	Zoledronic acid	IV	0.1 mg/kg	36 rabbits	bic	Turkey
2010	Koka S. et al.	re	Alendronate	Oral	70 mg/kg	137 patients	is	USA
2005	Kopman J.A. et al.	ex	Aminoguanidine and Doxycycline	SC	7.35 mmol/kg Aminoguanidine and 16.67 mg/kg Doxycycline	32 rats	bic	USA
1994	Jacobsson S.A. et al.	ex	Diclofenac	IM	30 mg/kg diclo	10 rabbits	bic	Sweden
2014	Giro G.	ex	Amoxicillin	Oral	40 mg/kg	35 rats	bic	Brazil
2006	Gabet Y.	ex	PTH	SC	5, 25 and 75 µg/kg	37 rats	bic	Israel
2010	Soares E.V. et al.	ex	Nicotine and Alcohol	SC	Diluted 10% ethanol and 0.125 mg/100 g Nicotine	20 rats	bic	Brazil
2004	Bombonato-Prado K.F. et al.	ex	Alcohol	Oral	10°, 15°, 20°, 25°, and 30° GL Brandy	112 rats	bic	Brazil
2012	Yip J.K. et al	re	Alendronate, Ibandronate, and Risedronate, Tiludronate, and Etidronate	Oral	nr	337 patients	is	USA
2011	Kim J.H. et al.	ex	Alendronate	SC	5 mg kg	24 rats	bic	South Korea
2010	Carvas J.S. et al.	ex	Methylprednisolone and Zoledronic acid	SC and IV	0.35 mg/kg Methylprednisolone and 0.1	18 rabbits	bic	Brazil

					mg/kg Zoledronic acid			
2017	Dikicier S. et al	ex	Zoledronic acid	IV	0.04 mg /kg	36 rats	bic	Turkey
2003	Narai S. and S. Nagaha ta	ex	Alendronate	SC	70 µg/kg	25 rats	bic	Japan
2005	Bobyn J.D. et al.	ex	Zoledronic acid	IV	0.1 mg/kg	7 dogs	bic	Canada
2017	Oliveira D. et al.	ex	Alendronate	Oral	0.1 mg /kg	42 rat	bic	Brasil
2006	Ribeiro F.V. et al.	ex	Meloxicam	SC	3 mg/kg	31 rat	bic	Brazil
1995	Kitsugi T. et al.	ex	Disodium Diphosphonate	SC	5.0, 2.5, 1.0, and 0.1 mg/kg	30 rabbit	bic	Japan
2013	Chen B. et al.	ex	Zoledronic acid, Alendronate, and Strontium ranelate.	Oral, and IV	0.1 mg/kg Zoledronic acid, 500 mg/kg Strontium ranelate, and 7 mg/kg Alendronat e	60 rat	bic	China
2009	Alissa R. et al.	rct	Ibuprofen	Oral	600 mg/kg	61 patients	is	UK
2012	Qi M. et al.	ex	Zoledronate acid	SC	0.1 mg/kg	56 rabbit	bic	China
2015	Virdi A.S. et al.	ex	Sclerostin Antibody	SC	25 mg/kg	161 rats	bic	USA
1998	Minsk L. and A.M. Polson	re	Hormonal replacement therapy	NR	nr	380 women	is	USA
2009	Faense n B. et al.	ex	Aprotinin	IV	7,200 KIU	40 rat	bic	Germany
1999	Ekelund A. et al.	ex	Cyclosporin A	Intrape ritonea l	2 mg/kg	24 rat	bic	Sweden
2016	Wang M. et al.	ex	Oxytocin	SC	1 mg/kg	20 rat	bic	China

2012	Dvorak G. et al.	ex	Vitamine D	Oral	2400 IU/kg	50 rat	bic	Austria
2003	Shih L.Y. et al.	ex	Estrogen therapy	SC	20 µg/kg	32 dog	bic	Tuiwun
2018	Linden M.S.S. et al.	ex	Nicotine	SC	3 mg/kg	22 rabbit	bic	Brazil
2010	Berley J. et al.	ex	Nicotine	SC	6 mg/kg	30 rat	bic	USA
2006	Eberhardt C. et al.	ex	Ibandronate	SC	1.0, 2.5, or 5.0 µg/kg	88 rats	bic	Germany
2009	Mair B. et al.	ex	PTH	SC	60 µg/kg	40 rats	bic	Austria
2008	Viera-Negron Y.E. et al.	ex	ald	subcut	5 mg/kg ALD 3 times a week.	32 rat in 4 groups: ALD-OVX n=8, OVX=8, ALD=8 and control =8	bic	USA
2015	Oh K.C.	ex	Alendronate	SC	1.0 mg/ kg	36 rats	bic	South Korea
2017	Wu X. et al.	re	PPI	NR	nr	799 patients	is	Canada
2018	Yang Q. and F.L. Li. Et al.	ex	Aspirin	NR	2.06, 4.11, 8.21 mg/kg	60 rats	bic	nr
2010	Dayer R.	ex	PTH or Pamidronate	SC	40 µg/kg PTH 0.6 mg/kg Pamidronate	41 rats	bic	Switzerland
2017	Dundar S. et al	ex	Zoledronic Acid	NR	0.1 and 2 mg/kg	12 rabbits	bic	Turkey
2005	Kurth A.H. et al	ex	Ibandronate	SC	1.0 or 25 µg/kg	84 rats	bic	Germany
1997	Young D.R. et al.	ex	Cisplatin	IV	75 mg/m2	24 dogs	bic	USA
2004	Qi M.C. et al.	ex	Benzyl estradiol	SC	20 µg/kg	60 rats	bic	China
2017	Xiong Y.	ex	Vitamine D	Intraperitoneal	5µg/kg	40 mice	bic	China
2012	Li Y. et al.	ex	Strontium ranelate	Oral	625 mg/kg	20 rats	bic	China

2004	Ayukawa Y. et al.	ex	Simvastatin	Intraperitoneal	10 mg/kg	10 rats	bic	Japan
2016	dos Santos R.A. et al.	ex	PTH	SC	2 or 40 µg/kg	50 rats	bic	Brazil
2011	Carvas J.B. et al.	ex	Methotrexate	IM	3 mg/kg	Four groups of 6-8 rabbits each	bic	Brazil
2008	Feitosa Dda S. et al.	ex	Thyroid hormonre	Oral	800 µg sodium l-thyroxine and 180 µg sodium triiodothyronine/1 L	42 rats	bic	Brazil
2012	Daugaard H. et al.	ex	PTH	SC	5 µg/kg	20 dogs	bic	Denmark
2016	Maiquan W. et al.	ex	Oxytocin	SC	1 mg/kg	20 rats	bic	China
2005	Eberhardt C. et al.	ex	Ibandronate	SC	1 or 25 µg/kg	52 rats	bic	Germany
2012	Ayan M. et al.	ex	Zoledronic acid	SC	0.1 mg/kg	12 rabbits	bic	Turkey
2012	Tsetsenekou E. et al.	ex	Alendronate	Oral	10 mg/kg	32 rabbit	bic	Austria
2017	Serrao C.R. et al.	ex	Metformin	Intraperitoneal	40 mg/kg	30 rats	bic	Brazil
1993	Sennerby L. et al.	ex	Indomethacin	SC	1 or 4 mg/kg	6 rabbits	bic	Sweden
2015	Mozzati M.	re	Alendronate, Risedronate, and Ibandronate	Oral	nr	235 patients	is	Italy
2006	Chacon G.E. et al.	ex	Alendronate	Oral	10 mg/kg	20 rabbits	bic	USA
2011	Daugaard H. et al.	ex	PTH	SC	5 µg/kg/	20 dogs	bic	Denmark
2001	Frenkel S.R. et al.	ex	Alendronate	SC	2.5 µg/kg	16 dogs	bic	USA

2011	Skoldenberg O.G. et al.	rct	Risedronate	Oral	35 mg/kg	73 patient	is	Sweden
2006	Sakakura C.E. et al.	ex	Cyclosporin A	SC	10 mg/kg	18 rabbit	bic	Brazil
2010	Li Y. et al.	ex	17β-estradiol	SC	20 µg/kg	20 rats	bic	China
2014	Wu X. et al.	re	SSRI	NR	nr	490 patients	is	Canada
1996	Werner S.B. et al.	ex	Dexamethasone	Intraperitoneal	120 µg/kg	9 rats	bic	Argentina
2010	Martin D.C. et al.	re	Alendronate, Risedronate, and Ibandronate	Oral	10 or 4 to 6 mg/kgAlendronate	16 patients	is	USA
2010	Yamano S. et al.	ex	Nicotine	SC	6 mg/kg	44 rats	bic	USA
2009	Basarir K. et al.	ex	Simvastatin	SC	50 mg/kg	20 rabbits	bic	Turkey
2006	Eberhardt C. et al.	ex	Ibandronate	SC	25 µg/kg	55 rats	bic	Germany
2005	Sakakura CE. et al.	ex	Cyclosporin A	SCe	10 mg/kg	18 rabbits	bic	Brazil
2016	Tao ZS. et al.	ex	PTH	SC	60 mg/kg	50 rats	bic	Zhejiang, china
2017	Salduz A. et al.	ex	Celecoxib and Diclofenac	Diclofenac IMly and Celecoxib oral	5 mg/kg Diclofenac Na and 3 mg/kg Celecoxib	40 rabbits	bic	Turkey
2008	Bell BM. et al.	re	Alendronate,Risedronate, or Ibandronate.	Oral	nr	42 patients	is	USA
2003	Cesar-Neto JB. et al.	ex	Nicotine	Inhalation or SC	3 mg/kg	45 rats	bic	Brazil
2008	Spence G. et al.	ex	Zoledronic acid	IV	0.05 mg/kg	12 sheep	bic	England
1995	Jeffcoat MK, et al.	rct	Flurbiprofen	IV	50 or 100 mg/kg	29 patients	bic	USA
1995	Cook SD, et al.	ex	Indomethacin	Oral	1 mg/kg	26 dogs	bic	USA

2012	Fahlgren A., et al.	ex	PTH	SC	20 µg/kg	104 rabbits	bic	Sweden
2016	Bastos MF., et al.	ex	Metformin	Oral	40 mg/kg	20 rats	bic	Brazil
2016	Heo HA., et al.	ex	PTH	SC	30 mg/kg	27 rats	bic	South Korea
2013	de Oliveira MA., et al.	ex	Zoledronic acid and Dexamethasone	SC	7.5 µg/kg Zoledronic acid and 1 mg/kg Dexamethasone	27 rats	bic	Brazil
2010	Yin H., et al.	ex	Simvastatin	SC	3.0 or 6.0 mg/kg	15 dogs	bic	China
2012	Sakka S	pr	ibuprofen	NR	600 mg/kg	28 patients	bic	Saudi Arabia
2007	Jensen TB	ex	Alendronate	Oral	0.5 mg/kg	16 dogs	bic	Denmark
2011	Famili P., et al.	re	Bisphosphonates	Oral	nr	211 women	bic	USA
2015	Yang X., et al.	ex	PTH	SC	40 µg/kg	90 mice	bic	USA
2007	Dayer R., et al.	ex	PTH or Pamidronate	SC	40 µg/kg PTH or 0.6 mg/kg Pamidronate	49 rats	bic	Switzerland
2008	Du Z	ex	Simvastatin	Oral	5 mg/kg	54 rats	bic	China
2001	Skripitz R., et al.	ex	PTH	SC	60 µg /kg	28 rats	bic	Sweden
2015	Xue Y., et al.	ex	PTH	SC	40 µg/kg	8 dogs	bic	China
2016	Al-Subaie AE., et al.	ex	Propranolol	SC	5 mg/kg	24 rats	bic	Canada
2011	Kuchler U., et al.	ex	PTH	SC	60 µg/kg	40 rats	bic	Austria
2011	Kuchler U., et al	rct	PTH	SC	20 µg/kg	24 patients	bic	Austria
2014	Winnet t B., et al.	re	NSAID (ibuprofen and ASA), Non-NSAID (Ketorolac, Vioxx, Celebrex, Diflunisal, Meloxicam,	NR	nr	168 patients	is	Canada

			Acetaminophen, and Naproxen					
2015	Cho PG., et al.	pr	PTH or Alendronate	PTH SC and Alendronate oral	20 µg/kg PTH or 91.37 mg/kg/week Alendronate	47 patients	Is	South Korea
2016	Al Subaie A	ex	PPI	Intraperitoneal	5 mg/kg	24 rats	bic	Canada
1995	Callahan BC., et al.	ex	warfarin	oral	0, 5, and 7.5 mg/kg	18 goats	bic	USA
2011	Zahid TM., et al.	re	Bisphosphonates	NR	5, 35, or 70 mg/kg	362 patients	is	USA
2002	Nociti FH., et al.	ex	Calcitonin and Estradiol	SC	16 IU/Kg Calcitonin or 20 µg/Kg 17β estradiol	58 rats	bic	Brazil
2018	Altug HA., et al.	ex	Hyperbaric oxygen	Inhalation	10 sessions of HBO treatment (each session lasted 90 minutes with exposure to 2.5 ATM of pure oxygen)	32 rabbits	bic	Turkey
2010	Chen BL., et al.	ex	Alendronate and Calcitonin	Alendronate oral,Calcitonin SC	7 mg/kg Alendronate and 5 IU/kg Calcitonin	40 rats	bic	China
2015	Tao ZS., et al.	ex	PTH or Simvastatin	NR	PTH 60 µg/kg and 5 mg/kg Simvastatin	50 rats	bic	China
2001	Duarte PM., et al.	ex	Cyclosporin A and nifedipine	SC	10 mg/kg Cyclosporin A and 0.5 mg/kg Nifedipine	28 rabbits	bic	Brazil
2017	Oki Y., et al.	ex	PTH	SC	40 µg/kg	15 rabbits	bic	Japan

2004	Skoglund B.,et al	ex	Ibandronate	Subcut or locally applied	3 µg /kg	76 rats	bic	Sweden
2012	Lima LL., et al.	ex	PTH and Nicotine	SC and inhalation	40 µg/Kg	48 rats	bic	Brazil
2011	Giro G., et al.	ex	Alendronate and estrogen	NR	Alendronate 50 µg/Kg or 17b-estradiol 20 µg/Kg	66 rats	bic	Brazil
2003	Siqueira JT. et al.	ex	Insulin	SC	2 IU	43 rats	bic	Brazil
2017	Oh KC., et al.	ex	Alendronate	SC	1.0 mg/kg	36 rats	bic	South Korea
2007	Giro G., et al.	ex	Alendronate and 17B Estradiol	SC	20 mg/kg 17b-estradiol and 50-µg/Kg Alendronate	58 rats	bic	Brazil
2016	Al-Mahalawy H., et al.	ex	Cisplatin	Intraperitoneal	2.5 mg/kg	16 rabbits	bic	Saudi Arabia
2017	Jin Y. et al.	ex	Lithium chloride	Oral	150 mg/kg	27 rats	bic	China
2015	Al Subaie AE., et al.	ex	Ranibizumab, anti-vascular endothelial growth factors (VEGF)	Intraperitoneal	15 µg/Kg Ranibizumab or 4 µg/Kg anti-VEGF	36 rats	bic	Canada
2016	Tao ZS., et al.	ex	PTH or Simvastatin	NR	40 µg/Kg PTH or 25 mg/kg Simvastatin	40 rats	bic	China
2008	Giro G., et al.	ex	Estrogen, and Alendronate	SC	17B-estradiol 20 µg/Kg or 50 µg/Kg Alendronate	66 rats	bic	Brazil
2012	Zhou C., et al.	ex	Vitamin D	Oral	0.1 µg/Kg	20 rats	Push-out force,bic	China
2013	Li YF., et al.	ex	PTH and local Zoledronic acid	SC	60 µg/kg	50 rats	bic	China
2005	von Knoch	ex	Zoledronic acid	SC	Single injection	28 mice	bic	Germany

	M., et al.				dose of 25 µg/kg			
2002	Astrand J. et al.,	ex	Alendronate or Clodronate	SC	3.8, 21, 205 µg/kg Alendronate or 0.12, 21 mg/kg Clodronate	111 rats	bic,	Sweden
2005	Eberhardt C., et al.	ex	Ibandronate	SC	1, 5 and 25 µg/kg	69 rats	bic	Germany
1989	Trancik	ex	Indomethacin, aspirin, and ibuprofen	SC	Indomethacin 2 mg/kg aspirin 17 mg/kg Ibuprofen I7 mg/kg	120 rabbits	bic	USA
2014	Hazzaa HH., et al.	ex	Alendronate	Oral	10 mg/kg	34 rabbits	bic	Egypt
2013	Maus UM., et al.	ex	Dihydrotestosterone	NR	1 mg/kg	20	bic	Germany
2017	Fu SH	re	Alendronate, Ibandronate, and Zoledronate	NR	nr	140067 patients	is	Taiwan
2017	Yukizawa Y., et al.	rct	Alendronate or Vitamin D	Oral	5 mg/kg Alendronate and Vitamin D 1 µg/kg	60 patients	is	Japan
2015	Cankaya D. et al.	ex	Alendronate, Risedronate, Calcitonin, indomethacin	SC	0.2 mg/kg Alendronate, 0.1 mg/kg Risedronate, 2 IU/kg salmon Calcitonin, and 4 mg/kg Indomethacin	30 rats	bic, push-out strength	Turkey
2015	Jaroma AV., et al.	rct	Alendronate	Oral	10 mg/kg	26 patients	is	Finland
2014	Prieto-alhambra D., et al.	re	Oral bisphosphonate	Oral	nr	80342 patient	Effect of oral bisphosphonates on total	Netherlands

							knee and hip implant survival.	
2014	Inoue G., et al.	pr	PTH	SC	20 or 56.5 µg/kg	29 women	bic, torque force	Japan
2010	Xue Q., et al.	ex	Alendronate	Oral	10 mg/kg	22 pigs	Bic, torque force	Denmark
2013	Nyberg J., et al.	ex	Hyperbaric oxygen	Inhalation	75-L pressure chamber (Göteborgs Dykeriteknik) and subjected to pure oxygen at 2.80 kPa absolute pressure for 2 hours two times daily	16 rats	bic, removal torque tests	Sweden
2014	Conte neto N., et al	ex	Alendronate	Oral	1 mg/kg	48 rats	Bic, removal torque tests	Brazil
2013	Ji WP., et al.	pr	Alendronate and Xianlinggubao	Oral	70 mg/day Alendronate and three capsules Xianlinggubao	80 patients	is	China
2013	Ohtori S., et al.	pr	PTH or Risedronate	SC PTH, Oral Risedronate	20 µg/kg PTH or 2.5 mg Risdronate	62 women	is	Japan
2012	Arnala IO., et al.	rct	Calcitonin (thyroid hormone replacement)	Nasal spray	200 IU	60 patients	is	Finland
2012	Liu S., et al.	ex	Sclerostin antibody	SC	25 mg/kg	36 rats	bic, pull-out test	USA
2013	Scott DF., et al.	rct	Zoledronic acid	IV	5 mg/kg	51 patient	is	USA

2013	Lübbeke A., et al.	pr	Statins	Oral	nr	735 patient	is	USA
2012	Virdi AS., et al.	ex	Sclerostin antibody	SC	25 mg/kg	90 rats	bic, pull-out test	USA
2012	Oliveira PA., et al.	ex	Hyperbaric oxygen	Inhalation	10 sessions Pure oxygen at 2.0 atmospheric absolute pressure (ATA) was applied for 90 min. per day for 10 days	48 rats	bic	Brazil
2013	Du Z., et al.	ex	Simvastatin	Oral	5 mg/kg	54 rats	bic	Australia
2011	Li CY., et al.	ex	Alendronate	Intraperitoneal	nr	27 rabbits	Bic, torque-out force	China
2011	Iwamoto N., et al.	pr	Alendronate or Vitamin D	Oral	5 mg/kg Alendronate or 1 µg/kg Vitamin D	60 patients	is	Japan
2011	Guimarães RP., et al.	ex	Aminoguanidine	intraperitoneal	10 - 20 mg/kg	36 rats	Bic and Biomechanical torque force	Brazil
2011	De deco CP., et al.	ex	Alcohol	Oral	20% ethanol solution	96 rats	Bic	Brazil
2011	Huja SS., et al.	ex	Zoledronic acid	IV	0.1 mg/kg	12 dogs	Bic	USA
2011	Huja SS., et al.	ex	Zoledronic acid	IV	0.1 mg/kg	4 dogs	Bic	USA
2010	Tapanin en TS., et al.	pr	Alendronate	Oral	10 mg/kg	16 patients	is	Finland
2010	Ayukawa Y., et al.	ex	Simvastatin	Intraperitoneal	0.125, 1, 5, or 10 mg/kg	60 rats	Bic	Japan
2009	Kelly J., et al.	ex	Vitamin D	NR	nr	28 rats	Bic and push-in test	USA

2009	Skripitz R., et al	ex	Alendronate and intermittent PTH	SC	PTH 60 µg/kg or 200 µg/kg Alendronate	36 rats	Bic	Sweden
2010	Hayashi K., et al.	ex	Prostaglandin EP4 receptor agonist (ONO-4819)	SC	30 µg/kg	26 rats	Bic and push-out test	Japan
2009	Hansson U., et al.	rct	Alendronate	Oral	70 mg/kg	60 patients	is	Sweden
2009	Blazsek J., et al.	ex	Aminobisphosphonate (Zoledronate)	Intraperitoneal	0.6 mg/kg	10 rats	Bic	Hungary
2009	Meunier A.et al.	rct	Celecoxib	Oral	200 mg/kg	50 patients	is	Sweden
2009	Friedl G., et al.	rct	Zoledronic acid	IV	4 mg/kg	50 patients	is	Austria
2008	Chen M., et al.	ex	Alendronate	Oral	10(-4) or 10(-5) mol/L Alendronate	36 rats	Bic	China
2008	Ohkawa, Y., et al.	ex	PTH	NR	30 µg/kg	81 rats	Bic and push-out tset	Japan
2008	Nogueira-Filho Gda, R., et al.	ex	Cannabis sativa	Inhalation	8 min/day	30 rats	Bic	Brazil
2008	Johansson HR., et al.	ex	PTH and Pamidronate	SC	60 µg/kg PTH and 500 µg/kg Pamidronate	138 rats	Bic and pull-out test	Sweden
2008	Aspenberg P., et al.	ex	PTH and ocal Pamidronate	NR	nr	48 rats	Bic and pull-out test	Sweden
2007	Søballe K., et al.	ex	Alendronate	Oral	0.5 mg/kg	16 dogs	Bic and push-out tests	USA
2008	Goodship AE., et al.	ex	Zoledronate	IV	10 µg/kg	12 Sheep	Bic	Switzerland
2008	Ma B., et al.	ex	Simvastatin	Oral and Local application	5, 10 or 50 mg/kg	162 rats	Bic and push out tests	UK

2007	Yamasaki S., et al.	pr	Risedronate	Oral	2.5 mg/kg	43 patients	is	Japan
2007	Nishioka T., et al.	pr	Alendronate	Oral	5 mg/day	17 patients	is	Japan
2006	Xing Z., et al.	ex	Pamidronate	intraperitoneal	0 – 40 µg/kg	25 rats	Bic	USA
2006	Hilding, M., et al.	rct	Coldronate	Oral	1.16 g/kg	50 patients	is	Sweden
2007	Moroni, A., et al.,	pr	Alendronate	Oral	70 mg/kg	16 patients	is	Italy
2006	McCracken, M.S., et al.,	ex	Insulin	SC	Insulin pellet	152 rats,	Bic	USA
2006	Fokter, S. K., et al.,	rct	Etidronate	Oral	400 mg/kg	31 patients	is	Slovenia
2006	Kinov, P., et al.,	pr	Risedronate	Oral	35 mg/kg	24 patients	is	Bulgaria
2005	Persson P. E., et al.,	pr	NSAID	Ibuprofen	400 mg/kg	96 patients	is	Sweden
2005	Wise, L. M., et al.,	ex	Zoledronate	SC	2 or 10 µg/kg	30 dogs	bic	Canada
2005	Balatsouka, D., et al	ex	Nicotine	SC	3 µg/kg	16 rabbits	Bic and removal torque test	Sweden
2005	Hayashi, K., et al.,	ex	Prostaglandin EP4 receptor agonist (ONO-4819)	subcut	15 µg/kg	84 rats	Bic and push-out test	Japan
2005	Virolainen, P., et al.,	ex	Doxorubicin, Cisplatin, and Ifosfamide	IV	20 mg/m2 doxorubicin, 50 mg/m' cisplatin, and 300 mg/m' of ifosfamide	8 dogs	Bic and removal torque test	USA
2006	Hossein K., et al.	re	Phenoxymethyl penicillin	Oral	2 g	868 patients	is	Sweden
2004	Peichl P., et al.	pr	Calcitonin	Nasal spray	200 IU	75 women	is	Austria

2004	Miyaji T., et al.	ex	Alendronate	SC	350 µg/kg	18 rats	Bic	Japan
2004	Koo S., et al.	ex	Alcohol	Oral	Brandy with 20% ethanol	9 rabbits	Bic	Brazil
2003	Margonar R., et al.	ex	Insulin	SC	10 U/day	27 rabbits	Bic and removal torque test	Brazil
2003	Nehme A., et al.	rct	Alendronate	Oral	10 mg/kg	38 patients	Bic	France
2003	Duarte P. M. et al.	ex	17beta estradiol and Calcitonin	SC	20 µg/kg of 17beta estradiol or 16 IU/kg of Calcitonin	58 rats	Bic	Brazil
2003	Wang C. J., et al.	rct	Alendronate	Oral	10 mg/kg	96 patient	is	Taiwan
2003	Zou X., et al.	ex	Alendronate	Oral	10 mg/kg	18 pigs	Bic	Denmark
2003	Tokugawa Y., et al	ex	Bisphosphonate (YM-175) and 17beta-estradiol pellet	SC	10 µg/kg	72 rats	Bic	Japan
2002	Soininvaara T. A., et al.	rct	Alendronate	Oral	10 mg /kg	19 patients	is	Finland
2002	Iwase M., et al.	ex	Bisphosphonate (TRK-530)	SC	1 mg/kg	40 rats	Bic	Japan
2002	Hennigs T., et al.	rct	Alendronate	NR	10 mg/kg	66 patients	Bic	Germany
2002	Stefani C. M., et al.	ex	Nicotine	SC	0.37, 0.57, and 0.93 mg/kg	32 rabbits	Bic	Brazil
2002	Millett P. J., et al.	ex	Alendronate	SC	0.01 mg/kg	72 rats	Bic	USA
2002	Thadani P. J., et al.	ex	Alendronate	SC	70 µg/kg	24 rats	Bic	USA
2001	Skripitz R., et al.	ex	PTH	SC	60 µg/kg	20 rats	Bic	Sweden
2001	Skripitz R., et al.	ex	PTH	SC	60 µg/kg	38 rats	Bic and pull-out test	Sweden

2001	August M., et al.	re	estrogen replacement therapy	NR	nr	526 patients	is	USA
2001	Zhang X., et al.	ex	Celecoxib	Oral	10 or 25 mg/kg	12 mice	Bic	USA
2001	Wilkinson J. M.	rct	Pamidronate	IV	90 mg/kg	47 patients	is	UK
2000	Hilding M., et al.	rct	Clodronate	Oral	400 mg/kg	50 patient	is	Sweden
1999	Wang X.	ex	Alendronate	Oral	6 mg/kg	16 dogs	Bic	USA
1999	Astrand J, et al.	ex	Alendronate	SC	0.063 mg/kg	48 rats	Bic	Sweden
1998	Fujimoto T., et al.	ex	Prednisolone	IM	10 mg/kg	12 rabbits	Bic and removal torque test	Japan
1989	Keller J. C., et al.	ex	NSAID (Indomethacin)	SC	10 mg/kg	30 rabbits	Bic	USA
2018	Suzuki T., et al.	pr	PTH	SC	56.5 µg/wk	34 patients	is	Japan
2017	Huang T. W., et al.	pr	Zoledronic acid	IV	5 mg/kg	60 patients	is	Taiwan
2016	Kaneko T., et al.	pr	PTH	SC	nr	40 patients	Bic	Japan
2015	Wu F. Q., et al.	ex	Zoledronic sodium	SC	0.1 mg/kg	30 rats	Bic	China
2016	Kobayashi N., et al.	rct	Teriparatide or Aldondrenate	SC of PTH and Oral of Alendronate	20 µg/kg PTH or 35 mg/kg Alendronate	48 patients	is	Japan
2015	Muren O., et al.	rct	Risedronate	Oral	35mg /kg	61 patients	is	Sweden
2014	Inouye K. A. S., et al.	ex	Metformin	Oral	100 mg/kg	36 rats	Bic	USA
2014	El-Kholey K. E., et al.	rct	antibiotic (Amoxicillin)	Oral	1 g	80; no AB, single dose, or 3 days	is	Saudi Arabia
2013	Lee J. K., et al.	pr	Aldendronate	Oral	70 mg/kg	61 Patients	is	South Korea

2013	Wu Y. Y., et al.	ex	vitamin D and insulin	Oral	12 µg/kg of vitamine D and 5.5 UI at 20:00 hours and 3.5 UI at 8:00 hours) of insulin	30 rats	Bic and push-out test	China
2012	de Molon R. S.,et al.	ex	Insulin	SC	100 U/ml	80 rats	Bic and removal torque test	Brazil
2012	Lee J. K., et al.	re	Aldendronate	Oral	70 mg/kg	82 patients	is	South Korea
2011	Lima C. C., et al.	ex	Alcohol	Oral	5% and 15% ethanol	15 rats	Bic	Brazil
2010	Esposito M., et al.	rct	Antibiotics (Amoxicillin)	Oral	2 g/kg	506 patients	is	UK
2011	Caiazzo A., et al.	rct	Antibiotics (Amoxicillin)	Oral	1 or 2 g/kg	100 patients	is	Italy
2011	El Hadary A. A., et al.	ex	Cyclosporin A and ozonated plant	SC Cyclosporin A and topical ozonated plant	10 mg/kg	20 rabbits	Bic	Egypt
2010	Trevisan C., et al.	rct	Clodronate	IM	100 mg	104 patients	is	Italy
2009	Gotfredsen K., et al	ex	Nicotine	SC	6 µg/kg	20 rabbits	Bic and removal torque test	Sweden
2009	De Morais J. A. N. D., et al.	ex	Insulin	SC	100 U/ml	40 rats	Bic	Brazil
2008	Arabmotlagh M., et al.	pr	Alendronate	NR	nr	49 patients	is	Germany

2006	Wang C. J., et al.	rct	Alendronate	Oral	10 mg	60 patients	is	Taiwan
2005	Bragdon C. R., et al.	ex	Alendronate	Oral	5 mg	12 dogs	Bic	USA
2005	Kwon P. T., et al.	ex	Insulin	NR	nr	32 rats	Bic	USA
2003	Duarte P. M., et al.	ex	Cyclosporin A plus nifedipine	SC	CsA (10 mg/kg) plus nifedipine (50 mg/kg)	28 rabbits	Bic	Brazil
2003	Sakakura C. E., et al.	ex	Cyclosporin A	SC	10 mg/kg	18 rabbits	Bic and removal torque test	Brazil
2001	Shibutani T., et al.	ex	Pamidronate	IM	0.6 mg/kg every	10 dogs	Bic	Japan
2017	Chrcanovic B.R.	re	SSRI	NR	nr	300 patients	is	Sweden
2011	Urdaneta et al.,	re	NSAID	NR	Aspirin 81, 162.2, and 325 Ibuprofen 400, 600 or 800-1600 Rofecoxib 25 mg Diclofenac 150 mg Celecoxib 200 mg Nabumetone 500 mg Naproxen 375 mg Etodolac 400 mg	81 patients	is	USA
2017	Chrcanovic BR., et al	re	PPI	NR	nr	999 patients	nr	Sweden

Appendix C: Quality assessment of animal studies

Table 8: SYRCLE's guidelines assessments for included articles of animal studies

Author	Selection bias			Performance bias		Detection bias		Attrition bias	Reporting bias	Other	Quality
	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding	Random outcome assessment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	
Toshiaki Kitsugi	no	yes	no	no	no	no	no	yes	no	no	-0.6
Lars Sennerby	no	no	no	no	no	no	no	no	no	no	-1
David R. Young,	no	no	no	no	no	no	no	yes	no	yes	-0.6
Anders Ekelund	unclear	no	no	no	yes	yes	yes	unclear	no	no	-0.2
Sally R. Frenkel	no	unclear	no	no	no	no	yes	yes	yes	no	-0.3
Satoru Narai	no	no	no	no	no	no	no	no	no	no	-1
Lih-Yuann Shih	unclear	yes	no	no	no	yes	no	yes	no	no	-0.3
Yasunori Ayukawa	no	no	no	no	no	no	no	no	no	no	-1
M.-C. Qi	unclear	yes	no	yes	no	yes	no	no	no	no	-0.3
J. D. Bobyn,	no	no	no	no	no	no	yes	no	yes	no	-0.6
A.H.A. Kurtha,	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Christian Eberhardt	unclear	yes	no	yes	no	no	no	yes	no	no	-0.3
Christian	unclear	yes	no	yes	no	no	no	yes	no	no	-0.3

Eberhardt,											
Guillermo E. Chacon	unclear	yes	no	yes	no	no	yes	yes	yes	no	0.1
Fernanda V. Ribeiro	unclear	yes	yes	yes	yes	yes	yes	no	yes	no	0.5
Celso E. Sakakura	unclear	yes	no	yes	no	yes	no	yes	yes	no	0.1
Christian Eberhardt1	unclear	yes	no	yes	no	no	no	unclear	no	no	-0.4
Kerem Başarır	no	no	no	no	no	no	no	yes	no	no	-0.8
B. Faensen	unclear	yes	no	unclear	yes	yes	yes	yes	no	no	0.2
Daniela da Silva Feitosa	unclear	yes	no	no	no	yes	no	no	no	no	-0.5
Yeritxa E. Viera-Negro´n	no	yes	yes	no	yes	yes	yes	no	yes	yes	0.4
Birgit Mair	unclear	no	no	no	no	yes	no	no	no	no	-0.7
R. Dayer	no	yes	no	no	no	no	no	no	no	no	-0.8
Yunfeng Li	no	yes	no	no	no	no	no	no	no	no	-0.8
Joel Berley	no	no	no	no	no	no	no	no	no	no	-1
Seiichi Yamano	no	no	no	no	no	no	yes	no	no	no	-0.8
H. Daugaard	unclear	no	no	no	no	yes	yes	no	no	no	-0.5
Efstathia Tsetsenekou	unclear	yes	no	no	no	no	yes	no	no	no	-0.5

Janaina Badin Carvas	no	no	no	no	no	no	yes	yes	no	no	-0.6
Mengchun Qi	no	yes	no	yes	no	yes	no	no	no	no	-0.4
Yunfeng Li	unclear	yes	no	yes	no	no	yes	yes	no	no	-0.1
Gabriella Dvorak	unclear	yes	no	no	no	no	no	no	no	no	-0.7
M Ayan	unclear	yes	no	yes	no	no	no	yes	no	no	-0.3
Henrik Daugaard,	unclear	yes	no	yes	yes	yes	yes	yes	yes	unclear	0.6
B. Chen	unclear	yes	no	no	no	yes	yes	yes	yes	no	0.1
KC Oh	no	no	no	no	no	no	no	yes	no	no	-0.8
Amarjit S. Virdi	unclear	yes	no	no	no	no	yes	yes	no	no	-0.3
Rodrigo A. B.	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Maiquan Wang	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Danila de OLIVEIRA	no	yes	no	no	no	no	no	no	no	no	-0.8
Serkan Dundar	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Yi Xiong	no	no	no	no	no	no	no	no	no	no	-1
Maria Salete Sandini Linden	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Stephen D. Cook	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
BERT C. CALLAHAN.	unclear	yes	no	no	no	no	no	no	no	no	-0.7
R. Skripitz	unclear	yes	no	no	yes	no	yes	yes	no	no	-0.1

Poliana M. Duarte	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Jörgen Åstrand	no	no	no	no	yes	no	yes	yes	no	no	-0.4
Bjorn Skoglund	yes	yes	yes	no	yes	no	yes	yes	yes	no	0.4
Marius von Knoch	no	yes	no	no	no	no	no	yes	no	no	-0.6
Celso Eduardo Sakakura	unclear	yes	no	no	yes	yes	yes	yes	no	no	0.1
Thomas B. Jensen	unclear	yes	no	no	yes	no	yes	yes	no	no	-0.1
Romain Dayer	no	yes	no	no	no	no	no	no	no	no	-0.8
Gabriela Giro	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Iwase, M., et al.,	unclear	yes	no	unclear	yes	unclear	yes	no	unclear	unclear	0.1
Millett, P. J., et al.,	yes	yes	no	no	yes	unclear	yes	yes	unclear	unclear	0.3
Inouye, K. A., et al.,	no	yes	no	unclear	unclear	no	no	unclear	yes	no	-0.3
Wu, Y. Y., et al.,	no	yes	no	no	no	no	no	unclear	unclear	no	-0.6
El Hadary, A.A., et al.,	yes	yes	no	yes	no	unclear	no	no	unclear	no	-0.2
Kwon, P. T., et al.,	no	yes	no	no	no	no	no	unclear	no	no	-0.7
Shibutani, T., et al.,	no	yes	no	no	no	no	no	no	unclear	no	-0.7

José T. Siqueira	no	yes	no	no	no	no	no	no	no	no	-0.8
Sakakura, C. E., et al.,	unclear	yes	yes	yes	no	no	no	yes	yes	no	0.1
Zhang, X., et al.,	no	yes	yes	no	no	no	no	yes	yes	no	-0.2
Lima, C. C., et al.	unclear	yes	yes	yes	no	no	no	no	yes	no	-0.1
de Molon, R.S., et al.,	unclear	yes	yes	yes	no	no	no	yes	yes	no	0.1
Keller, J. C., et al.	no	yes	no	no	no	no	no	no	yes	no	-0.6
Stefani, C. M., et al	unclear	yes	yes	yes	no	yes	no	no	yes	no	0.1
Duarte, P. M., et al.,	no	yes	no	yes	no	no	no	no	no	no	-0.6
Skripitz, R., et al.,	unclear	yes	no	no	no	yes	yes	no	no	no	-0.3
Deniz Cankaya 1	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Nicolau Conte Neto	unclear	yes	no	no	no	no	yes	no	no	no	-0.5
Shuo Liu	no	no	no	no	no	no	no	no	no	no	-1
Amarjit S. Virdi	unclear	yes	no	no	no	no	no	yed	yes	no	-0.4
Oliveira PAD	unclear	yes	no	no	no	no	yes	yes	no	no	-0.3
Zhibin Du	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Guimara ̃es RP	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Sarande ep S. Huja	no	no	no	no	no	no	yes	yes	no	no	-0.6

Sarandeep S. Huja	no	yes	no	no	no	no	yes	yes	no	no	-0.4
Y. AYUKAWA	no	no	no	no	no	no	no	no	no	no	-1
James Kelly	no	yes	no	no	no	no	no	no	no	no	-0.8
Qingyun Xue	unclear	yes	no	no	no	yes	yes	yes	no	no	-0.1
K. Hayashi	no	yes	no	no	no	no	no	no	no	no	-0.8
József Blazsek	no	yes	no	no	no	no	no	no	no	no	-0.8
Getulio da R. Nogueira-Filho	unclear	yes	no	no	no	no	yes	yes	no	no	-0.3
H. R. Johansson	unclear	yes	no	no	yes	yes	yes	yes	no	no	0.1
Per Aspenberg	yes	yes	no	no	yes	no	yes	yes	no	no	0
Kjeld Søballe	no	yes	no	no	no	yes	yes	yes	no	no	-0.2
Allen E. Goodship	unclear	yes	no	no	no	no	yes	no	no	no	-0.5
Bingkui Ma	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Zhiqing Xing	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
L. M. Wise	no	yes	no	no	yes	no	yes	no	no	no	-0.4
Dimitra Balatsouka	no	yes	no	no	no	no	no	no	no	no	-0.8
K. Hayashi	yes	yes	no	no	yes	no	no	no	no	no	-0.4
Samuel Koo	no	yes	no	no	no	no	no	no	no	no	-0.8

Poliana Mendes Duarte	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
THOMAS TRANCI	no	no	no	no	no	no	no	no	no	no	-1
SVEN-ARNE JACOBSSON,	yes	yes	no	no	no	no	no	yes	no	no	-0.4
Fiorellini JP,	no	no	no	no	no	no	no	yes	no	no	-0.8
Stuart Goodman	no	yes	no	no	no	no	yes	no	no	no	-0.6
Tatsuo Shirota	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Karina Fittipaldi Bombonato-Prado	no	yes	no	no	no	no	yes	no	no	no	-0.6
Poliana Mendes Duarte,	unclear	yes	no	no	no	no	yes	yes	no	no	-0.3
Jeffrey A	unclear	no	no	no	no	yes	yes	yes	no	no	-0.3
Dimitra Balatsouka	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Yankel Gabet	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Birgit Mair	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Alethe´ia B. Pablos	unclear	yes	no	no	no	no	yes	no	no	no	-0.5
By Yoshinari Nakamura	no	yes	no	no	no	no	no	no	no	no	-0.8
Marcelo Soeiro Corsini	unclear	yes	no	no	no	no	no	no	no	no	-0.7

Fernanda Vieira Ribeiro	unclear	yes	no	no	no	no	yes	no	no	no	-0.5
Evelise V.	no	no	no	no	no	no	no	yes	no	no	-0.8
J. S. B. Carvas	no	yes	no	no	no	no	no	no	no	no	-0.8
Yunfeng Li,	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Laurent Maïmoun	no	no	no	no	no	no	no	no	no	no	-1
Alper Yıldız	unclear	yes	no	no	no	yes	no	yes	no	no	-0.3
Per Aspenberg	unclear	no	no	no	yes	no	yes	yes	no	no	-0.3
Henrik Daugaard	unclear	yes	no	no	no	yes	yes	yes	no	no	-0.1
J-H Kim	no	yes	no	no	no	no	no	yes	no	no	-0.6
M. Isabel Almagro	no	yes	no	no	no	yes	no	no	no	no	-0.6
Ferhan Yaman	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Jian-Ping Li	no	yes	no	no	no	no	no	yes	no	no	-0.6
InSoo Kim	no	yes	no	no	no	no	no	yes	no	no	-0.6
Gabriela Giro	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Emre Dikicier	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Wei Xin Cai	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Mario Henrique A.	unclear	yes	no	no	no	no	yes	yes	no	no	-0.3
Magnus Bernhardsson	unclear	yes	no	no	no	no	yes	yes	no	no	-0.3

G. Ramalho-Ferreira	no	yes	no	no	no	no	no	no	no	no	-0.8
Tina Rybaczek	unclear	no	no	no	no	no	no	no	no	no	-0.9
Zheng X,	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Sibel Dikicier	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Letícia Pitol PALIN	no	no	no	no	no	no	no	no	no	no	-1
João B. César-Neto	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Gabriela Giro	unclear	yes	no	no	no	no	no	no	no	no	-0.7
G. Spence	no	no	no	no	no	no	yes	no	no	no	-1
Zhibin Du	yes	yes	no	no	no	no	no	no	no	no	-0.6
B.-L. Chen	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Gabriela Giro	no	yes	no	no	no	no	no	no	no	no	-0.8
Ulrike Kuchler	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Han Yin	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Anna Fahlgren	no	no	no	no	no	no	yes	no	yes	no	-0.77
Liana Linhares Lima	unclear	yes	no	no	no	no	yes	yes	no	no	-0.44
Chenchen Zhou	unclear	yes	no	no	no	no	no	no	no	no	-0.7
Y. F. Li &	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Marcio A. de Oliveira	unclear	yes	no	no	no	yes	yes	yes	no	no	-0.22

Al Subaie A	unclear	yes	no	yes	yes	no	yes	yes	no	no	0
Xu Yang	no	yes	no	no	yes	no	yes	yes	no	no	-0.33
Zhou-Shan Tao	unclear	yes	no	no	no	YES	no	yes	no	no	-0.3
Zhou-Shan Tao	no	yes	no	no	yes	no	yes	yes	no	no	-0.33
Hyun-A Heo	no	yes	no	no	no	no	no	no	no	no	-0.8
Al Subaie A	yes	yes	no	no	yes	no	yes	yes	no	no	0
Zhou-Shan Tao	unclear	yes	no	no	no	yes	no	yes	no	no	-0.3
Haytham Al-Mahalawy	unclear	yes	no	no	no	no	no	yes	no	no	-0.5
Marta Ferreira Bastos	unclear	yes	no	no	no	no	yes	yes	no	no	-0.3
Al-Subaie AE	yes	yes	no	no	yes	no	yes	yes	no	no	0
Yifan Jin	yes	yes	no	no	no	no	no	no	no	no	-0.6
Kyung Chul Oh	no	yes	no	no	no	no	no	yes	no	no	-0.6
Ahmet Salduz	yes	yes	no	no	no	no	no	yes	no	no	-0.4
Yoshifumi OK	no	yes	no	no	no	no	no	no	no	no	-0.8
Hasan Ayberk ALTUG	yes	yes	no	no	no	no	yes	yes	no	no	-0.2
Thadani, P. J., et al.,	no	no	no	no	no	no	no	no	no	no	-1

Skripitz, R., et al.,	unclear	yes	yes	no	no	yes	no	yes	yes	no	0.1
Wang, X., et al.,	unclear	yes	yes	no	no	yes	no	no	no	no	-0.3
Gotfredsen, K., et al.,	no	yes	no	no	no	no	no	no	no	no	-0.8
de Morais, J. A., et al.,	unclear	yes	yes	no	no	no	yes	yes	no	no	-0.1
Bragdon, C. R., et al.,	no	yes	no	no	no	no	no	yes	no	no	-0.6
Caroline Ribeiro Serrão et al.	unclear	yes	yes	no	no	no	yes	yes	yes	yes	0.3
Astrand, J., et al.,	no	yes	no	no	no	no	no	no	yes	no	-0.6
Fujimoto et al	no	yes	no	no	no	no	no	no	yes	no	-0.6
F. H. Nociti Jr., et al.	unclear	yes	no	no	no	no	no	no	yes	no	-0.5
Werner SB1, et al.	no	yes	no	no	no	no	no	no	yes	no	-0.6
Nociti FH Jr, et al.	no	yes	no	no	no	no	no	no	yes	no	-0.6
HazzaaHH,Amin et al.	unclear	yes	no	no	no	no	no	yes	yes	no	-0.3
Nyberg J,Hertzm et al.	no	yes	no	no	no	no	yes	yes	yes	no	-0.2
de Deco CP,da et al.	no	yes	no	no	no	no	no	yes	yes	no	-0.4
Ohkawa Y,Tokunaga et al.	no	yes	no	no	no	no	no	no	yes	no	-0.6

McCracken MS, et al.	no	yes	no	no	no	no	no	yes	yes	no	-0.4
Virolainen P,et al.	no	yes	no	no	no	no	no	yes	yes	no	-0.4
Miyaji T et al.,	no	yes	no	no	no	no	no	yes	yes	no	-0.4
Margonar R, et al,.	unclear	yes	no	no	no	no	no	no	yes	no	-0.5
Zou X,Xue Q, et al,	unclear	yes	no	no	no	yes	yes	no	yes	no	-0.1
Tokugawa Y,et al,	unclear	yes	no	no	no	no	no	no	yes	no	-0.5
Skripitz R1, Aspenberg P.	unclear	yes	no	no	no	yes	yes	yes	yes	no	0.1

Appendix D: Quality assessment of RCTs

Table 8: Cochrane risk of bias assessments for included articles of randomized controlled trials RCTs

Auther	Random sequence generation	Allocation concealment	Selection Reporting	other Bias	Blinding of Participants and Personal	Blinding of outcome assessment	incomplete outcome data	Quality
LIonberger D R.,	unclear	high	low	unclear	unclear	unclear	low	poor
Duka M.,	low	high	low	unclear	high	high	unclear	poor
Alissa R.,	low	low	low	low	low	low	low	Good
Sköldenberg OG	low	low	low	low	low	low	low	Good
Jeffcoat MK	unclear	unclear	low	high	unclear	unclear	low	poor
Kuchler U	low	unclear	low	low	high	unclear	high	poor
Yukizawa Y	low	unclear	low	low	unclear	unclear	high	poor
Jaroma AV	unclear	low	low	unclear	low	unclear	low	poor
Arnala IO	unclear	unclear	low	low	high	high	low	poor
Scott DF	unclear	unclear	low	unclear	high	high	low	poor
Hansson U	low	low	low	unclear	low	low	low	Good
Meunier A	low	low	low	low	low	unclear	unclear	fair
Friedl G	unclear	low	low	low	low	low	low	Good
Hilding M	unclear	unclear	unclear	low	unclear	unclear	unclear	poor
Fokter SK	low	low	low	low	low	low	low	Good
Wilkinson JM	low	low	unclear	low	unclear	unclear	unclear	poor
Esposite Marco	low	low	low	low	low	low	low	good
Trevisan C	low	unclear	low	unclear	high	high	low	poor
Wang CJ	high	unclear	low	unclear	unclear	unclear	unclear	poor
Kobayashi Naomi	low	unclear	low	unclear	unclear	unclear	unclear	poor
Wang	high	unclear	low	low	high	unclear	low	poor
Muren	unclear	unclear	low	low	high	high	low	poor
Wang, C. J.,	high	unclear	low	unclear	high	high	low	poor
Maria Hilding	unclear	unclear	low	low	low	unclear	low	fair
El-Kholey KE,	low	unclear	low	unclear	low	unclear	low	poor
Caiazzo A,	low	unclear	low	high	high	high	low	poor

Appendix E: Quality assessment of observational studies

Table 9: STROBE quality assessment for the included studies of observational studies

First Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	result
Avedian RS	0	1	0	1	0	1	0	1	1	0	1	0	0	0	1	0	1	0	1	0	0	0	high
Kasai T	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	high
Kova´cs AF	1	1	1	0	1	1	0	1	0	1	1	0	1	0	1	0	0	1	1	0	0	0	moderate
Vassilis Petsinis,	1	1	1	1	0	1	0	0	0	1	0	0	1	0	1	0	0	1	1	1	0	1	moderate
Daniel Prieto-Alhambra,[a]	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	0	1	1	1	1	1	1	low
Memon S,	1	1	1	0	0	0	1	1	1	0	0	0	1	1	1	0	0	0	0	0	0	0	high
Bao-Thy Grant,	1	1	1	1	1	1	0	0	0	1	0	0	0	1	1	0	0	1	0	0	0	0	high
Siebert T,	1	1	1	1	0	1	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	high
Fugazzotto PA,	1	1	1	1	1	1	1	1	0	0	0	0	0	1	1	0	0	1	0	0	0	0	moderate
Wu X	1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	0	0	1	low
Koka S	1	1	1	1	1	1	0	0	1	1	0	0	1	1	0	0	0	1	1	1	0	0	moderate
Mozzati M	1	1	1	1	0	1	0	0	0	0	0	1	1	1	1	1	1	1	0	1	0	0	moderate
Wu X	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	low
Daniel C. Martin	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	0	1	1	1	0	0	moderate
Brian M.	1	1	1	1	0	1	1	1	0	1	0	0	0	0	1	0	0	1	1	0	0	0	moderate
Sakka S	0	1	1	0	0	1	1	1	0	0	1	0	1	0	1	1	1	1	0	1	0	0	moderate
Famili P.	1	1	1	1	1	0	0	0	1	1	0	0	1	0	1	1	0	1	0	1	0	0	moderate
Brent Winnett	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	1	1	1	0	1	0	0	moderate
Pyung Goo Cho	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	low
Talal M. Zahid	1	1	1	1	1	1	0	0	0	1	0	1	1	1	1	1	0	1	1	1	0	1	moderate
Fu SH,	1	1	1	1	1	1	1	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	moderate
Prieto-Alhambra D[b]	1	1	1	1	1	1	1	0	1	0	1	1	1	1	0	0	1	0	0	0	0	1	moderate
Ji WP,	0	1	1	0	0	1	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	high
Ohtori S,	1	1	1	1	1	1	0	1	0	0	0	0	1	1	1	0	0	1	1	0	0	0	moderate
Lübbeke A,	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1	0	1	low
Iwamoto N,	0	1	1	0	0	1	1	1	0	0	0	0	0	0	1	0	0	1	1	0	0	1	high
Tapaninen TS,	1	1	1	1	1	1	0	0	0	0	0	0	1	0	1	0	0	1	0	1	0	0	high
Yamasaki S,	0	1	1	0	0	1	0	1	0	0	0	0	0	0	1	0	0	1	1	0	0	0	high
Nishioka T,	0	1	1	0	0	1	0	1	0	0	0	0	0	1	1	0	0	1	0	0	0	0	high

Moroni A,	1	1	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	high
Persson PE,	1	1	1	1	1	0	1	1	0	1	1	0	1	1	1	1	0	1	0	0	0	0	moderate
Kashani H,	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	high
Peichl P,	0	1	1	1	0	0	0	1	0	0	0	0	1	1	1	0	0	1	0	0	0	0	high
August M,	1	1	1	1	0	1	1	1	0	1	0	0	1	0	1	1	1	1	1	1	0	0	moderate
Suzuki T,	1	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	high
Huang TW,	1	1	1	1	0	0	0	1	1	0	0	0	1	1	1	0	0	1	1	0	0	1	moderate
Kaneko T,	1	1	1	0	0	1	1	1	0	1	0	1	1	1	1	0	0	1	0	1	0	0	moderate
Lee JK,	0	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	0	0	moderate
Arabmotlagh M	1	1	1	1	0	1	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	high
Yip JK	1	1	1	1	1	1	0	0	0	1	0	0	0	0	1	1	0	1	1	1	0	0	moderate
Minsk L,	1	1	1	1	1	0	0	1	0	0	0	0	1	1	1	0	0	1	1	0	0	0	moderate
Wu X [b]	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	low
Gen Inoue	1	1	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	high
Knov et al,	1	1	1	1	1	1	1	1	0	1	1	1	0	0	1	1	0	1	1	1	1	0	moderate
Chrcanovic BR	1	1	1	1	1	1	1	0	0	0	1	0	1	1	1	0	0	1	1	0	0	1	moderate
Rainier A.	1	1	1	1	1	0	0	0	0	0	0	0	0	0	1	0	0	1	1	0	1	0	high
Ramos B	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	1	1	0	1	low
Jin Kyu Lee	1	1	1	1	1	0	1	1	0	1	0	0	1	0	1	0	0	1	1	1	1	1	moderate