UNIVERSIDADE FEDERAL FLUMINENSE

FACULDADE DE ODONTOLOGIA

O IMPACTO DA TERAPIA COM BISFOSFONATOS NO DESEMPENHO DE IMPLANTES DENTÁRIOS: UMA *OVERVIEW* DA EVIDÊNCIA DE REVISÕES SISTEMÁTICAS

Niterói

2018

UNIVERSIDADE FEDERAL FLUMINENSE

FACULDADE DE ODONTOLOGIA

O IMPACTO DA TERAPIA COM BISFOSFONATOS NO DESEMPENHO DE IMPLANTES DENTÁRIOS: UMA *OVERVIEW* DA EVIDÊNCIA DE REVISÕES SISTEMÁTICAS

VIVIAN VIVEIROS MENDES

Dissertação apresentada à Faculdade de Odontologia da Universidade Federal Fluminense, como parte dos requisitos para obtenção do título de Mestre, pelo Programa de Pós-Graduação em Odontologia.

Área de Concentração: Clínica odontológica

Orientador: Prof. Dr. Vittorio Moraschini

Niterói

2018

FICHA CATALOGRÁFICA

Ficha catalográfica automática - SDC/BNO

M538i Mendes, Vivian Viveiros
O impacto da terapia com bisfosfonatos no desempenho de implantes dentários: uma overview da evidência de revisões sistemáticas / Vivian Viveiros Mendes ; Vittorio Moraschini, orientador. Niterói, 2018.
49 p.

Dissertação (mestrado)-Universidade Federal Fluminense, Niterói, 2018.

DOI: http://dx.doi.org/10.22409/PPGO.2018.m.10598506721

1. Odontologia baseada em evidências. 2. Implantes dentários. 3. Bisfosfonato. 4. Osteonecrose. 5. Produção intelectual. I. Título II. Moraschini,Vittorio, orientador. III. Universidade Federal Fluminense. Faculdade de Odontologia.

CDD -

Bibliotecária responsável: Lúcia Espogeiro - CRB7/4708

BANCA EXAMINADORA

Prof. Dr. Vittorio Moraschini

Instituição: Faculdade de Odontologia (Departamento de Periodontia) da Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brasil

Decisão: _____Assinatura:_____

Prof. Dr. Edgard de Mello Fonseca

Instituição: Faculdade de Odontologia (Departamento de Prótese) Universidade Federal Fluminense, Niterói, Rio de Janeiro, Brasil

Decisão: _____Assinatura:_____

Prof. Dr. Gonçalo Sobreira Pimentel Neto

Instituição: Odontoclínica Central da Marinha (Clínica de Implantodontia), Rio de Janeiro, Brasil

Decisão: _____Assinatura:_____

DEDICATÓRIA

Dedico esta, bem como todas as minhas demais conquistas, aos meus amados pais que sempre confiaram em mim e nunca tiveram a pretensão de que eu chegasse até aqui. E, claro, ao meu marido, pessoa com quem amo partilhar a vida.

AGRADECIMENTOS

A Deus, autor do meu destino.

À Universidade Federal Fluminense, pela oportunidade.

Ao meu orientador, Vittorio, que com carinho, paciência e extrema competência tornou possível a conclusão deste trabalho. Obrigada pela sua capacidade de me trazer paz na agitação de cada dúvida que surgia.

Ao meu chefe, Gonçalo, pelo incentivo e pelo apoio constantes. Sem sua ajuda para tornar possível a minha presença em cada aula, eu não teria concluído este curso. Desejei a sua participação na banca examinadora deste trabalho desde o início.

Aos amigos e professores Mônica Zaccharias, Edgard Fonseca e Laila Zarranz, meus primeiros incentivadores no mundo acadêmico ao longo da monitoria no Curso de Prótese Fixa. Eu posso dizer que a minha formação não teria sido a mesma sem vocês. É um prazer ter um representante de vocês na minha banca examinadora.

E a todos aqueles que de alguma forma estiveram e estão próximos de mim, fazendo esta vida valer cada vez mais a pena. Gratidão.

RESUMO

Mendes VV. O impacto da terapia com bisfosfonatos no desempenho de implantes dentários: uma *overview* da evidência de revisões sistemáticas [dissertação]. Niterói: Universidade Federal Fluminense, Faculdade de Odontologia; 2018.

O objetivo deste trabalho foi avaliar métodos, qualidade e resultados de revisões sistemáticas que investigam cientificamente o impacto dos bisfosfonatos em implantes dentários e o risco de desenvolver osteonecrose dos maxilares relacionada a bisfosfonatos após a cirurgia de implante dentário. Uma pesquisa eletrônica, sem restrição de data ou idioma, foi realizada no PubMed/MEDLINE, Cochrane, *Web of Science* e LILACS até janeiro de 2018. Os critérios de inclusão foram revisões sistemáticas que avaliaram o impacto dos bisfosfonatos nos resultados dos implantes. A avaliação da qualidade dos estudos incluídos foi realizada utilizando as diretrizes do AMSTAR 2. O protocolo desta *overview* foi registrado no PROSPERO sob o número CRD42018089617. O processo de busca e seleção resultou em 7 estudos, publicados entre 2009 e 2017. Nenhuma das revisões sistemáticas incluídas no estudo obteve pontuação máxima nas análises de qualidade realizadas. Evidências científicas disponíveis demonstraram que pacientes com histórico de tratamento com bisfosfonatos não apresentam um risco maior de falha do implante dentário ou perda óssea marginal em comparação com pacientes que não utilizaram bisfosfonatos. A literatura também sugere que pacientes que se submetem a trauma cirúrgico durante a instalação de implantes dentários podem ser mais suscetíveis à osteonecrose dos maxilares relacionada aos bisfosfonatos.

Palavras-chave: Odontologia baseada em evidências, implantes dentários, bisfosfonato, osteonecrose dos maxilares relacionada a bisfosfonatos, taxa de sobrevivência.

ABSTRACT

Mendes VV. The impact of bisphosphonate therapy on dental implant outcomes: An overview of the systematic review evidence [dissertation]. Niterói: Universidade Federal Fluminense, Faculdade de Odontologia; 2018.

The purpose of this overview was to assess methods, quality, and outcomes of systematic reviews conducted to evaluate the impact of bisphosphonates on dental implants and the risk of developing bisphosphonate-related osteonecrosis of the jaw after dental implant surgery. An electronic search without date or language restriction was carried out in PubMed/MEDLINE, Cochrane, Web of Science, and LILACS until January 2018. Eligibility criteria included systematic reviews that evaluated the impact of bisphosphonates on implant outcomes. The quality assessment of the included studies was performed using AMSTAR 2 guidelines. The protocol of this overview was registered in PROSPERO under the number CRD42018089617. The search and selection process yielded 7 studies, published between 2009 and 2017. None of the systematic review that were included in the study obtained the maximum score in the quality analyses performed. Available scientific evidence demonstrates that patients with a history of bisphosphonates use do not present a higher risk of dental implant failure or marginal bone loss compared to patients who have not used bisphosphonates. The literature also suggests that patients who undergo surgical trauma during the installation of dental implants may be more susceptible to bisphosphonate-related osteonecrosis of the jaw.

Keywords: Evidence-based dentistry, dental implants, bisphosphonate, bisphosphonate-related osteonecrosis of the jaw, survival rate.

1 - INTRODUÇÃO

Os bisfosfonatos (BFs), como o alendronato, risedronato, ibandronato e clodronato, são potentes drogas inibidoras de osteoclastos e são considerados a terapia de escolha para o tratamento de doenças que afetam o metabolismo ósseo, como a osteoporose, mieloma múltiplo, doença de Paget, hipercalcemia maligna e metástase óssea do câncer.[1] As duas principais categorias de BFs são as que não possuem nitrogênio, que são metabolizadas rapidamente; e BFs que contêm nitrogênio, que são mais potentes e não são metabolizadas. Uma vez depositado no osso, quantidades muito pequenas de BFs são liberadas na circulação durante a renovação celular. Consequentemente, a meia-vida de BPs no osso é estimada em anos.[2]

A abordagem terapêutica que inibe a atividade dos osteoclastos pode ser positiva em ortopedia e traumatologia para diminuir a reabsorção óssea e interferir na formação e crescimento de metástases ósseas. Por outro lado, a inibição dos osteoclastos e a alteração da microestrutura óssea podem ser indiretamente prejudiciais em implantodontia se o metabolismo ósseo for bloqueado, pois pode prejudicar a osseointegração dos implantes dentários.[3] No entanto, há relatos de que o uso local de BFs (revestimento superficial do implante e/ou aplicação direta no sítio cirúrgico) promove efeito positivo na formação óssea peri-implantar em animais[4-7] e na melhora da fixação de implantes osseointegrados em humanos.[8,9]

Um efeito adverso significativo observado em pacientes utilizando BFs orais ou intravenosas que foram submetidos a procedimentos odontológicos invasivos, como a terapia com implantes, é a osteonecrose dos maxilares relacionada a bifosfonatos (ONMB), que é clinicamente caracterizada por uma exposição dolorosa do osso na cavidade oral.[10] Algumas revisões sistemáticas (RSs)[11-13] relataram altas taxas de sobrevivência para implantes em pacientes tratados com BFs. No entanto, outros autores observaram uma relação entre BFs, falhas de implantes dentários e BRONJ.[14]

O objetivo deste trabalho foi avaliar os métodos, qualidade e resultados de RSs que investigam cientificamente o impacto de BFs no desempenho dos

implantes dentários e o risco de desenvolver ONMB após a cirurgia de implante dentário.

2 - METODOLOGIA

2.1 Registro de protocolo

O protocolo desta *overview* foi registrado no PROSPERO sob o número CRD42018089617. Não houve desvio do protocolo originalmente especificado no registro. Embora não seja uma RS, a metodologia básica do presente estudo seguiu as recomendações do *Cochrane Handbook for Systematic Reviews of Interventions.*[15] Os questionamentos clínicos realizados para a estratégia de busca foram organizados usando a estratégia PICOS.[16]

2.2 Questionamento principal (estratégia PICO)

Em pacientes sob terapia intravenosa (IV), oral ou local, qual é o impacto dos BFs no desempenho dos implantes dentários e qual é o risco de desenvolver ONMB?

2.3 Estratégia de pesquisa

Uma busca eletrônica sem restrição de data ou idioma foi realizada no PubMed/MEDLINE, Cochrane, *Web of Science* e LILACS até janeiro de 2018. Além disso, foi realizada uma busca eletrônica específica nas seguintes páginas virtuais das revistas: *Journal of Periodontology, Journal of Clinical Periodontologia*, Pesquisa Clínica de Implantes Orais, Implantodontia Clínica e Pesquisas Relacionadas, *International Journal of Oral & Maxillofacial Implants, International Journal of Oral & Maxillofacial Surgery e Implant Dentistry*. Uma pesquisa na literatura cinza nos bancos de dados *Gray Literature Report*[17] e *OpenGrey*[18] não revelou estudos publicados. Pesquisas em referências dos estudos incluídos (cruzamento de referências) também foram realizadas.

Termos de MeSH, palavras-chave e outros termos livres relacionados com “dental implants”, “osseointegrated implant”, “implant failure”, “implant survival”, “implant success”, “osteonecrosis”, “osteonecrosis of the jaw”, “bisphosphonate(s)”, “etidronate”, “clodronate”, “risedronate”, “alendronate”, “ibandronate”, “pamidronate”, and “zoledronic acid” foram usados com Operadores Lógicos Booleanos (OU, E) para combinar as buscas. A estratégia de busca incluiu mudanças apropriadas nas palavras-chave e seguiu as regras sintáticas de cada banco de dados.

2.3 Critérios de inclusão delineados de acordo com a população, intervenções/ exposição, comparações, resultados e desenho do estudo (estratégia PICOS)[16]

População: adultos (≥ 18 anos) em terapia com BFs (IV ou oral) que receberam implantes dentários.
Intervenções: Instalação de implantes dentários em pacientes em terapia com BF.
Comparação: Não realizada.
Resultado: O desfecho primário foi avaliar o impacto da terapia com BFs no desempenho dos implantes dentários. O resultado secundário foi avaliar a perda óssea marginal (POM) em torno de implantes dentários e o risco de desenvolver ONMB após a instalação do implante dentário.
Desenho do estudo: Revisões sistemáticas com ou sem meta-análise.

2.4 Processo de triagem

O processo de busca e triagem foi realizado por dois autores revisores independentes (V.M. e V.M.), iniciando com a análise de títulos e resumos. Em seguida, foram selecionados artigos completos para leitura criteriosa e analisados de acordo com critérios de elegibilidade (inclusão / exclusão) para futura extração de dados. Desacordos entre os autores da revisão foram resolvidos através de uma discussão cuidadosa. Quando necessário, os autores dos estudos incluídos foram contatados por e-mail para esclarecimento das dúvidas remanescentes.

2.5 Extração de dados

Quando disponíveis, os seguintes dados foram extraídos dos estudos incluídos por dois autores revisores independentes (V.M e V.M): autores, pergunta de pesquisa, número de estudos incluídos, resultados obtidos e resultados de meta-análises.

2.6 Avaliação da qualidade das revisões sistemáticas

A avaliação da qualidade das RS foi realizada de forma independente por dois autores revisores (V.M e V.M). A qualidade metodológica de cada RS foi avaliada com a ferramenta AMSTAR 2.[19] As diretrizes apresentam 16 itens que são classificados em quatro opções: 1 indica “sim”, 2 indica “não”, 3 indica “não pode responder” e 4 indica “não aplicável”. Somente os itens com opção 1 (“sim”) geraram pontuações. Portanto, cada artigo poderia obter uma pontuação entre 0 (nenhum critério) e 16 (todos os critérios).

2.7 Análise estatística

Os dados coletados por meio da ferramenta de avaliação de qualidade AMSTAR 2 foram analisados por estatística descritiva. A média e o desvio padrão da análise foram calculados. Todas as análises estatísticas foram realizadas utilizando Excel (Mac 2011, versão 14.0.0, Microsoft) e StatPlus (Mac LE.2009, AnalystSoft Inc.).

3 - ARTIGO PRODUZIDO

Evidence-based knowledge on the impact of bisphosphonate therapy on dental implant outcomes: An overview of the systematic review evidence

Vivian Mendes, DDS, MS
Department of Integrated Clinics, School of Dentistry, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil.

Gustavo Oliveira dos Santos, DDS, MS, Ph.D
Department of Integrated Clinics, School of Dentistry, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil.

Monica Diuana Calasans-Maia, DDS, MS, Ph.D
Department of Oral Surgery, School of Dentistry, Fluminense Federal University, Niterói, Rio de Janeiro, Brazil.

José Mauro Granjeiro, DDS, MS, Ph.D
National Institute of Metrology, Quality and Technology, Rio de Janeiro, RJ, Brazil; Cell Therapy Center, Clinical Research Unit and Biology Institute, Fluminense Federal University, Niterói, RJ, Brazil

Vittorio Moraschini, DDS, MS, PhD (Corresponding Author)
Department of Periodontology, School of Dentistry, Fluminense Federal University**.**
Rua Mario dos Santos Braga, 30, Centro, Niterói, Rio de Janeiro, Brazil. Cep.: 24020-140.
E-mail: vittoriomf@terra.com.br

Abstract

The purpose of this overview was to assess methods, quality, and outcomes of systematic reviews conducted to evaluate the impact of bisphosphonates on dental implants and the risk of developing bisphosphonate-related osteonecrosis of the jaw after dental implant surgery. An electronic search without date or language restriction was carried out in PubMed/MEDLINE, Cochrane, Web of Science, and LILACS until January 2018. Eligibility criteria included systematic reviews that evaluated the impact of bisphosphonates on implant outcomes. The quality assessment of the included studies was performed using AMSTAR 2 guidelines. The protocol of this overview was registered in PROSPERO under the number CRD42018089617. The search and selection process yielded 7 studies, published between 2009 and 2017. None of the systematic review that were included in the study obtained the maximum score in the quality analyses performed. Available scientific evidence demonstrates that patients with a history of bisphosphonates use do not present a higher risk of dental implant failure or marginal bone loss compared to patients who have not used bisphosphonates. The literature also suggests that patients who undergo surgical trauma during the installation of dental implants may be more susceptible to bisphosphonate-related osteonecrosis of the jaw.

Keywords: Evidence-based dentistry, dental implant, bisphosphonate, bisphosphonate-related osteonecrosis of the jaw, implant survival

Introduction

The bisphosphonates (BPs), such as alendronate, risedronate, ibandronate, and clodronate, are potent osteoclast inhibitor drugs and are considered the

first choice therapy in diseases affecting bone metabolism, such as osteoporosis, multiple myeloma, Paget's disease, hypercalcemia of malignancy, and cancer bone metastasis.[1] The two main categories of BPs are non-nitrogen-containing, which are metabolized rapidly, and nitrogen-containing BPs, which are more potent and not metabolized. Once deposited in bone, very small amounts of BPs are released into circulation during the turnover. Consequently, the half-life of BPs in bone is estimated in years.[2]

The therapeutic approach inhibiting osteoclast activity may be positive in orthopaedics and traumatology to diminish bone resorption and interfere with the formation and growth of bone metastases. On the other hand, the osteoclast inhibition and alteration of the bone microenvironment may be very indirectly deleterious in implant dentistry if bone metabolism is blocked because this can impair dental implant osseointegration.[3] However, there are reports that the local delivery of BPs (via implant surface coating and/or direct application to the surgical site) promotes a positive effect on peri-implant bone formation in animals[4-7] and on improving the fixation of osseointegrated implants in humans.[8,9]

A significant adverse effect observed in patients using either oral or intravenous BPs who have undergone invasive dental procedures, such as implant therapy, is bisphosphonate-related osteonecrosis of the jaw (BRONJ), which is clinically characterized by a painful exposure of bone in the maxillofacial region.[10] Some systematic reviews (SRs)[11-13] have reported high survival rates for implants in patients treated with BPs. However, other authors have observed a relationship between BPs, dental implant failures, and BRONJ.[14]

The purpose of this overview was to assess methods, quality, and outcomes of SRs conducted to evaluate the impact of BPs on dental implants and the risk of developing BRONJ after dental implant surgery.

Material and Methods

Protocol registration

The protocol of this overview was registered in PROSPERO under the number CRD42018089617. There was no deviation from the originally specified protocol as registered. Although not an SR, the basic methodology of the present study followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[15] The clinical questionings conducted for the search strategy were organized using the PICOS strategy.[16]

Focused question (PICO question)

In patients on intravenous (IV), oral, or local application, what is the impact of BPs on dental implant outcomes, and what is the risk of developing BRONJ?

Search strategy

An electronic search without date or language restriction was carried out in PubMed/MEDLINE, Cochrane, Web of Science, and LILACS until January 2018. Furthermore, a specific electronic search was performed on the following journals' websites: *Journal of Periodontology, Journal of Clinical Periodontology*, *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *The International Journal of Oral & Maxillofacial Implants*, *International Journal of Oral & Maxillofacial Surgery*, and *Implant Dentistry*. A

search of the Grey Literature Report[17] and OpenGrey databases[18] revealed unpublished studies (grey literature). Searches in references of the included studies (cross-referencing) were also conducted.

MeSH terms, keywords, and other free terms related to “dental implants”, “osseointegrated implant”, “implant failure”, “implant survival”, “implant success”, “osteonecrosis”, “osteonecrosis of the jaw”, “bisphosphonate(s)”, “etidronate”, “clodronate”, “risedronate”, “alendronate”, “ibandronate”, “pamidronate”, and “zoledronic acid” were used with Boolean operators (OR, AND) to combine searches. The search strategy included appropriate changes in the keywords and followed the syntactic rules of each database.

Inclusion criteria outlines according to the population, interventions/exposure, comparisons, outcomes, and study design (PICOS strategy)[16]

Population: adults (≥ 18 years) on BP therapy (IV or orally) who received dental implants.

Interventions: Installation of dental implants in patients on BP therapy.

Comparison: Not performed.

Outcome: The primary outcome was to evaluate the impact of BP therapy on dental implants’ survival. The secondary outcome was to assess the marginal bone loss (MBL) around dental implants and the risk of developing BRONJ after dental implant installation.

Study design: Systematic reviews with or without meta-analysis.

Screening process

The search and screening process was carried out by two independent reviewing authors (V.M. and V.M.), starting with analysis of titles and abstracts. Next, full papers were selected for careful reading and analysed according to eligibility criteria (inclusion/exclusion) for future data extraction. Disagreements between reviewing authors were resolved through careful discussion. When necessary, the authors of the included studies were contacted by email for clarification of remaining doubts.

Data extraction

When available, the following data were extracted from the included studies by two independent reviewing authors (V.M and V.M): authors, focused question, number of included studies, outcome measures, and meta-analysis results.

Quality assessment of the systematic reviews

The quality assessment of the SRs was conducted independently by two reviewing authors (V.M and V.M). The methodological quality of each SR was evaluated with the AMSTAR 2 tool.[19] The guidelines feature 16 items that are classified into four options: 1 indicates “yes”, 2 indicates “no”, 3 indicates “cannot answer”, and 4 indicates “not applicable.” Only items with option 1 (“yes”) generated scores. Therefore, each article could obtain a score between 0 (no criteria) and 16 (all criteria).

Statistical analysis

The data collected using the AMSTAR 2 quality assessment tool were analysed using descriptive statistics. The mean and standard deviation of the analysis were calculated. All statistical analyses were performed using Excel (Mac 2011, version 14.0.0, Microsoft) and StatPlus (Mac LE.2009, AnalystSoft Inc.).

Results

Literature search

The initial search resulted in 222 titles on MEDLINE/PubMed, one title on the Cochrane Central Register of Controlled Trials, 28 on Web of Science, and none on LILACS. The first evaluation resulted in the selection of 12 complete articles. After critical reading, five studies[20-25] were excluded because they did not meet the eligibility criteria of this study (Table 1). Thus, seven studies,[11-14,26-28] published between 2009 and 2017, were included in the current overview. A search of grey literature did not result in any additional studies. The process of searching for and selecting articles can be followed in Figure 1.

Study characteristics

The characteristics of the included studies are presented in Table 2. The selected SRs evaluated the BPs in three different routes of administration (oral,[11-14,26,28] IV,[11,12,14,26] and local[27]). The orally administered drugs were risedronate, ibandronate, and etidronate, while those administered intravenously were zoledronic acid, clodronate and pamidronate. The BP use periods prior to implant installation varied from three[11,14,26] to 192[12-14] months. The most commonly reported reasons for BP use were osteoporosis and

malignant neoplasm. The number of studies included in the SRs varied from three[27] to 21,[12] the majority using prospective and retrospective cohort design.

All included studies reported implant survival rates. Variations in survival rate from 89.2[12] to 100%[28] (cumulative average 94.8 ± 3.9) and 96.1[13] to 99.2%[28] (cumulative average 97.6 ± 1.13) were observed among the groups that did and did not use bisphosphonates by systemic routes, respectively. One study[27] evaluated only the use of BPs by the local route (surface of the implants), observing a survival rate of 91.3% for implants with BPs and 100% for implants without BPs.

Two SRs[11,13] evaluated the survival of implants through meta-analysis. Ata-Ali et al.'s meta-analysis[11] did not demonstrate a significant influence of BPs on implant survival (P = 0.156), while in the work of Chrcanovic et al.,[13] BPs had a significant influence (P = 0.003) on implant survival.

Of the seven studies included, only two[13,14] (28.5%) observed evidence for an increase in the number of dental implant failures in patients who used BPs (Table 3).

In the case of BRONJ, three SRs[12,14,26] observed a greater number of cases in patients who had been using BPs prior to implant installation compared with patients who had never used the medication (Table 3).

Only two SRs[13,27] analysed MBL. Chrcanovic et al.[13] did not observe a significant difference (P = 0.59) when they performed meta-analysis of MBL among patients who had used BPs when compared to patients who had never used BPs. Guimarães et al.[27] also did not observe evidence of greater MBL in patients who received local application of BPs during implant installation when compared to patients without BPs.

Quality assessment

None of the SRs included satisfied all AMSTAR 2 criteria (Table 4). The score varied from 5[28] to 14[13] points, with an average of 9.5 ± 3.2 out of a possible total of 16 points. Items 1, 7, 9, and 16 were scored as positive for all included reviews. Conversely, no review scored as positive for item 11. Four studies[11,13,14,27] (57%) reported having followed the PRISMA Statement[29] guidelines for the design of SRs.

Discussion

Summary of evidence

The present overview sought scientific evidence for the influence of BPs on the results of dental implant treatment. Although there are SRs on the subject, there is still no consensus in the literature on the actual impact of BPs on the performance of dental implants or on the risk of BRONJ occurrence. By aggregating only SR data, the present study is able to analyse the most convincing scientific evidence.[30]

BPs are potent inhibitors of osteoclast activity normally employed in the treatment of skeletal diseases such as primary and secondary osteoporosis and bone metastases.[31,32] As BPs interfere with the bone turnover process, this characteristic led to the hypothesis that such drugs could have a negative impact on the osseointegration process of dental implants. Furthermore, the surgical trauma of implant installation combined with a possible inhibition of the

bone turnover process could be related to a greater probability of the occurrence of BRONJ.[33]

Numerous case reports are detailed in the literature describing the use of BPs and complications in the installation of dental implants.[34-38] However, a blinded clinical trial evaluating complications in 50 participants (25 with a history of BP use and 25 with no history of use) did not observe a greater number of implant failures or BRONJ cases in the group of participants who used BPs.[39] Other cohort studies conducted also did not observe statistically significant differences regarding implant failures and BRONJ for participants who used BPs.[40,41]

Contrary to the hypothesis of BPs having a negative influence on dental implants, there are contemporary studies suggesting that BPs could have a supportive role in osseointegration by biomodulating the process of bone remodelling.[27] The positive effect of local use of BPs on osseointegration was demonstrated by preclinical studies on different animal models[42-45] and in an SR[27] of studies on humans included in the present overview.

Two works[11,13] included in the present study analysed the survival of implants using meta-analysis, observing divergent results. Ata-Ali et al.[11] expressed their results in terms of odds ratio (OR), and Chrcanovic et al.[13] in terms of relative risk (RR). The studies also differed in relation to the inclusion criteria and the numbers of studies included in the meta-analyses. These characteristics may have influenced the difference of results between the two SRs. Only prospective and retrospective cohort studies were included in the meta-analyses, which may have increased the risk of biased outcomes.[46,47] Therefore, the results should be analysed and interpreted with caution.

The cumulative average survival rate of implants observed in the groups of patients who used BPs was 94.8%, while in the groups with no BP use history it was 97.6%. Although the patients with no BP use history presented a lower number of implant failures, this difference was only considered significant in two of the included SRs.[13,14] A recently published SR evaluating the survival rate of dental implants in healthy patients observed a rate of 94.6% over an average of 13.4 years of followup.[42] These data are compatible when compared to the survival rate observed by this overview, thus not showing a greater number of failures in patients with a history of BP use.

Three SRs[12,14,26] observed a significant risk of BRONJ occurrence after implant installation in patients undergoing BP therapy. In two of these SRs[12,26] it was observed that the majority of BRONJ cases were related to more invasive procedures, such as bone regeneration procedures and installation of multiple implants. Chadha et al.[12] also observed a higher occurrence of BRONJ in studies that evaluated patients who had used BPs orally for a period of more than five years. Oral use for less than five years presented minimal cases.

None of the SRs reported a more prevalent BP administration route or a specific anatomical area (maxilla or mandible). Publications on BRONJ are normally in the form of case studies or case series. A lack of evidence of significant scientific impact was observed by all SRs investigating the relationship between BRONJ and dental implants. Thus, we still lack robust data associated with the occurrence of BRONJ after surgical trauma in patients who have used BPs.

Currently, the pathogenesis of BRONJ is debated, but with strong evidence of being multifactorial.[43] Factors such as reduction of bone turnover (inhibition of osteoclasts) with subsequent bone necrosis,[44] reduction in extracellular matrix

production by fibroblasts,[45] decreased angiogenesis,[46] and the toxic effect of BPs on mucosal tissue[47] are strongly associated with inflammatory and infectious processes (osteomyelitis) in the surgical area. In addition, genetic factors such as polymorphisms may also be associated with a greater susceptibility to developing BRONJ.[48]

Use of the marker test of carboxy-terminal telopeptide of type I collagen (CTX) has been proposed as a means to determine risk and prognosis for patients who have used BPs and will undergo jaw surgery.[49-51] Type I collagen is the main constituent of the extracellular organic matrix, and during bone resorption, CTX is released. However, a recent SR, after reviewing results from eight prospective studies, has shown that the use of CTX is not valid in determining the risk of BRONJ.[52]

Only two SRs evaluated MBL and did not observe a significant difference between patients with a history of BP use and with no history of use. Although Chrcanovic et al.'s SR[13] evaluated MBL using meta-analysis, only two studies (the minimum possible) were included in the analysis. The two studies included in the meta-analysis totalled 1461 implants (180 for BPs and 1281 for non-BPs), showing no statistically significant difference (P=0.59) for MBL. However, due to the limited number of studies included in the meta-analysis and the design of the studies (retrospective), this analysis should be interpreted with caution because of the possibility of a high risk of bias.

An average quality in SR methodology was observed during the analysis conducted (average of 9.5 points out of a total of 16 possible). Low sensitivity and limited scope (e.g., grey literature) and deficiency in the discussion and

incorporation of heterogeneity/risk of bias in the studies were commonly observed deficiencies.

Strengths and limitations

The present overview presents several strengths, such as a record of protocol, an unrestricted search of literature (including grey literature), and a duplicate review process for the search, data extraction, and quality analysis of the included studies. However, the present study has some limitations. Firstly, the vast majority of SRs included were conducted by analysing cohort studies (prospective and retrospective), case reports, and case series. These studies, when compared to controlled clinical trials, may present a greater potential risk of bias. Secondly, some SRs did not present individualised data by drug type, route of administration, and specific locations of implant failures, BRONJ, and MLB. This can make it difficult to analyse and interpret the data. In addition, the quality analysis conducted demonstrated numerous methodological shortcomings in the conduct of SRs.

Implications for clinical practice

The evidence does not demonstrate a considerable difference with respect to the survival of implants and MBL between patients who undergo BP therapy and those who do not. Thus, there appears to be no specific procedure regarding the successful osseointegration of dental implants. In contrast, current evidence shows a greater index of BRONJ cases in patients with a history of BP use. To date, there is no valid method for BRONJ risk analysis prior to surgical procedures. Therefore, clinical analysis should be individualised

and based on the route of administration of the drug, the period of conduct and termination of the treatment, and the expectation of surgical trauma.

In conclusion, the available scientific evidence demonstrates that patients with a history of BP use do not present a higher risk of dental implant failure or MBL compared to patients who have not used BPs. The literature also suggests that patients who undergo surgical trauma during the installation of dental implants may be more susceptible to BRONJ when compared to patients without a history of BP use. However, additional clinical studies are necessary for a better understanding of the risk factors.

Declarations

Funding: The authors declare that no funding was provided for the elaboration of this study.

Competing Interests: The authors declare that there was no conflict of interest during the elaboration of this study.

Ethical Approval: Not required – the study did not involve human subjects.

Patient Consent: Not required – the study did not involve human subjects.

Table 1. Excluded studies.

Reason for rejection	**Authors**
Narrative review	Shah et al.[21]; Thirunavukarasu et al.[22]; Javed and Almas[23]
Not focused exclusively on bisphosphonate and dental implant survival	Boquete-Castro et al.[20]
Included animal studies	Walter et al.[25]