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Lúcio Henrique Ives Martins

**RISCO DE OSTEONECROSE EM USUÁRIOS DE BISFOSFONATOS SUBMETIDOS
A PROCEDIMENTO ODONTOLÓGICO: REVISÃO SISTEMÁTICA E METANÁLISE**

Sorocaba/SP

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Dissertação apresentada à Banca Examinadora do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba, como exigência parcial para obtenção do título de Mestre em Ciências Farmacêuticas.

Orientadora: Profa. Dra. Cristiane de Cássia Bergamaschi

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Aprovado em:

BANCA EXAMINADORA:

Profa. Dra. Cristiane de Cássia Bergamaschi
Universidade de Sorocaba (UNISO)

Profa. Dra. Daiane Cristina Peruzzo
Faculdade de Medicina e Odontologia e Centro de Pesquisas
Odontológicas São Leopoldo Mandic

Profa. Dra. Flávia Martão Florio
Faculdade de Medicina e Odontologia e Centro de Pesquisas
Odontológicas São Leopoldo Mandic

Dedico este trabalho à toda minha família
e amigos que sempre estiveram ao meu
lado em todas as fases de minha vida.

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“Cada sonho que você deixa pra trás, é um pedaço do seu futuro que deixa de existir.”

Steve Jobs

RESUMO

Embora a osteonecrose oral seja considerada uma doença rara, quando manifestada, se mostra muito resistente às terapias de tratamento disponíveis e de difícil resolução clínica. Alguns procedimentos odontológicos podem ser fator de risco para desencadear esta condição em usuários de bisfosfonatos. Dados atualizados a respeito do risco deste efeito adverso em pacientes submetidos a intervenções odontológicas e em uso de bifosfonatos não foi encontrado na literatura. Este estudo determinou o risco de osteonecrose de maxilares em usuários de bisfosfonatos submetidos a intervenções odontológicas. Trata-se de uma revisão sistemática que usou as seguintes fontes de informação: MEDLINE (via Ovid), EMBASE (via Ovid), *Web of Science*, Scopus, Biblioteca Virtual da Saúde e Banco de teses da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), sem restrição de idioma ou data de publicação, com busca realizada até a data de 25 de agosto de 2020. A pergunta de pesquisa seguiu a estratégia PICO (População: indivíduos maiores de 18 anos em terapia com bisfosfonatos e submetidos a procedimentos cirúrgicos odontológicos e/ou trauma por prótese dental, e Desfecho: risco de osteonecrose de maxilares). Revisores, aos pares e independentemente, selecionaram os estudos, realizaram a extração de dados e avaliaram o risco de viés. O risco da osteonecrose em função da duração do tratamento com bisfosfonatos foi verificado. As metanálises foram agrupadas pelo modelo aleatório de DerSimonian e Laird. Foram incluídos 27 estudos e 4.865 pacientes, sendo a maioria mulheres e idosos. Os bisfosfonatos mais utilizados foram o zoledronato por via intravenosa ($n=17$ estudos) e o alendronato por via oral ($n= 19$), para tratamento de doenças oncológicas ($n= 11$) e osteoporose ($n= 16$), respectivamente. A extração dental foi o procedimento mais comum ($n= 21$). A maioria dos estudos apresentou baixa qualidade metodológica ($n= 21$). O risco de osteonecrose nos pacientes foi de 0,8% (IC 95% = 0,5-1,2%), sendo maior risco com o uso de bisfosfonato intravenoso [8,9% (IC 95% = 6,5-11,5%) comparado ao uso oral [0,0% (0,0-0,1%)]. Não foi observado maior risco de osteonecrose em função do tempo de tratamento ($p>0,05$). Concluiu-se que houve maior risco de osteonecrose oral em pacientes em uso de bisfosfonatos intravenosos e submetidos principalmente, a extração dental. Há necessidade de mais estudos com descrição detalhada dos bisfosfonatos e doses utilizadas. Esses achados contribuem para os pacientes, prescritores, cirurgiões-dentistas e outros

profissionais de saúde, a fim de orientar a respeito dos riscos de realizar intervenções odontológicas nestes pacientes.

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Palavras-chave: Osteonecrose de maxilares. Bisfosfonatos. Prevalência.Incidência.

Revisão sistemática.

ABSTRACT

Although osteonecrosis of jaw be considered a rare condition, it can be refractory to available treatment therapies and clinically difficult to manage. Some dental procedures can represent risk factor for triggering the condition in bisphosphonate users. No recent data on the risk of this adverse effect after dental interventions in bisphosphonate users were found in the literature. This study determined the risk of osteonecrosis of the jaw in bisphosphonate users undergoing dental interventions. This systematic review searched the following information sources: MEDLINE (via Ovid), EMBASE (via Ovid), Web of Science, Scopus, Virtual Health Library and Thesis Bank of the Coordination for the Improvement of Higher Education Personnel, with no restriction on language or publication date until August 25, 2020. The research question was devised according to the PICO strategy (Population: individuals over 18 being treated with oral bisphosphonate submitted to surgical dental procedures or interventions for trauma due to dental prosthesis; and Outcome: risk of osteonecrosis of the jaw). Reviewers, in pairs and independently, selected the studies, extracted their data and assessed risk of bias. The risk of osteonecrosis in relation to bisphosphonate treatment duration was determined. The meta-analyses were pooled using the DerSimonian and Laird random effects model. A total of 27 studies (4,865 patients) were included, with samples comprising predominantly females and older adults. The most used bisphosphonates were zoledronate by the intravenous route (n= 17 studies) and alendronate by the oral route (n= 19) for treating cancers (n= 11) or osteoporosis (n= 16), respectively. Dental extraction was the most common procedure (n= 21). Most of the studies had low methodological quality (n= 21). The risk of osteonecrosis in patients was 0.8% (95% CI: 0.5-1.2%), where higher risk was associated with the use of bisphosphonate intravenously [8.9% (95% CI= 6.5-11.5%) than orally [0.0% (95% CI= 0.0-0.1%)]. There was no association between longer treatment duration and greater risk of osteonecrosis ($p>0.05$). Results showed higher risk of osteonecrosis of jaw in intravenous bisphosphonate users submitted mainly, to dental extraction. Further studies are needed with a detailed description of bisphosphonates and doses used. These findings contribute to patients, prescribers, dentists and other health professionals, in order to provide guidance on the risks of performing dental interventions in these patients.

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Key-words: Osteonecrosis of the jaw. Bisphosphonates. Prevalence. Incidence. Systematic review.

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LISTA DE ABREVIATURAS E SIGLAS

AAOMS - *American Association of Oral and Maxillofacial Surgeons* (Associação Americana de Cirurgiões-dentistas)

ANVISA - Agência Nacional de Vigilância Sanitária

ASBMR - *American Society for Bone and Mineral Research* (Sociedade Americana de Investigação Óssea e Mineral)

BRONJ - *Bisphosphonate-related osteonecrosis of the jaw* (Osteonecrose dos Maxilares Associado ao Bisfosfonato)

CTX - *Type I Collagen Terminal C-Telopeptide* (Telopeptídeo-C Terminal do Colágeno tipo I)

CVS/SES/SP - Centro de Vigilância Sanitária da Secretaria Estadual de Saúde de São Paulo

EMA - *European Medicines Agency* (Agência Europeia de Medicamentos)

MS - Ministério da Saúde

MHRA - *Medicines and Healthcare Products Regulatory Agency* (Agência Reguladora de Medicamentos e Produtos de Saúde)

MRONJ - *Medication-Related Osteonecrosis of the Jaw* (Osteonecrose da Mandíbula Relacionada à Medicação)

HIV - *Human Immunodeficiency Virus* (Vírus da Imunodeficiência Humana)

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1 APRESENTAÇÃO

Esta disssertação trata-se de uma revisão sistemática com metanálise que determinou o risco da osteonecrose nos maxilares, também conhecida como osteonecrose maxilar e/ou mandibular, em usuários de bisfosfonatos submetidos a procedimentos odontológicos.

A osteonecrose é uma doença grave e rara ocasionada principalmente devido ao uso de medicamentos antirreabsortivos e antiangiogênicos. Este efeito adverso afeta a qualidade de vida dos pacientes. Embora não seja uma condição comumente observada, quando ocorre, é de difícil resolução clínica.

A osteonecrose de maxilares pode ser agravada em pessoas que utilizam bisfosfonatos e são submetidas à intervenção cirúrgica odontológica ou outras condições, como trauma causado pelo uso de prótese dentária. Os bisfosfonatos, grupo de fármacos antirreabsortivos, são principalmente utilizados no tratamento e na prevenção da osteoporose e no tratamento de doenças oncológicas.

Na literatura pesquisada não foi observada informação atualizada, por meio de revisão sistemática, a respeito do risco de osteonecrose de maxilares em usuários de bisfosfonatos submetidos à intervenção cirúrgica odontológica ou que tenha ocorrido devido à trauma por prótese dental.

Este achado é relevante para os prescritores, os cirurgiões-dentistas e outros profissionais de saúde, a fim de advertir para o risco devido ao uso de tais medicamentos e agravo pelo procedimento odontológico. Diante disso, estratégias podem ser elaboradas para minimizar o problema, considerando os seus impactos.

Para maior esclarecimento e organização, este trabalho foi estruturado em: Referencial teórico, Objetivos, Resultados e Considerações finais, seguindo as orientações do Programa de Pós-graduação em Ciências Farmacêuticas quanto a escrita da dissertação no formato de artigo científico (ANEXO 1).

O tópico “Referencial teórico” foi estruturado nos subtópicos: i) Osteonecrose oral e diagnóstico; ii) Diagnóstico diferencial; iii) Etiopatogênese da osteonecrose e o risco do uso dos bisfosfonatos; iv) Medicamentos antireabsortivos da classe dos bisfosfonatos; v) Outros medicamentos com potencial de causar osteonecrose oral; vi) Osteonecrose em usuários de bisfosfonatos e submetidos a procedimentos odontológicos; e vii) Prevenção e tratamento da osteonecrose dos maxilares.

O tópico “Objetivos” faz referência aos objetivos “primários” e “secundários” traçados por essa revisão.

O tópico “Resultados” foi estruturado com a produção científica desenvolvida, sendo apresentado o artigo científico, intitulado: “Risk of osteonecrosis in bisfosfonate users submitted to dental procedure: systematic review and meta-analysis”.

O tópico “Considerações finais” discorre sobre os achados e conclusões da presente dissertação.

As referências desta dissertação estão em uma lista única e final.

A declaração dos potenciais conflitos de interesses encontra-se no ANEXO 2.

2 REFERENCIAL TEÓRICO

2.1 Osteonecrose oral e diagnóstico

A osteonecrose é uma perda generalizada de tecido ósseo decorrente de fatores que levaram a morte celular. Pode ocorrer a qualquer local no sistema esquelético, mas geralmente envolve os ossos longos como fêmur, tíbia e úmero (THOMAS, 1993; YONEDA, 2017).

A osteonecrose oral ou osteonecrose de maxilares é uma condição rara caracterizada por exposição e perda óssea no complexo maxilofacial. Pode resultar em morbidade significativa e também ser resistente à terapia convencional (CAREY; PALOMO, 2008; CHIU *et al.*, 2018; DE ANTONI *et al.*, 2018).

Esta condição foi descrita no século XIX em operários expostos ao fósforo branco ou amarelo, usado na fabricação de palito de fósforo. Conhecida como "mandíbula phossy" ou "necrose de fósforo da mandíbula" era causada pelo vapor de fósforo que destrói os ossos da mandíbula e frequentemente resultou em grave despigmentação tecidual, osteonecrose e até morte. O uso do fósforo branco foi posteriormente banido em muitos países devido aos relatos desta doença (DONOGHUE, 2005).

Outra condição que evoluiu para a osteonecrose surgiu no início do século XX, com o uso da radioterapia para o tratamento de câncer de cabeça e pescoço. Entretanto, seus efeitos colaterais incluíam danos severos conhecidos como osteoradionecrose, descrita por LaDow, em 1950. O autor citou três principais causas de osteonecrose de maxilares sendo elas provocadas pelo uso da radioterapia, por trauma e/ou por infecção na cavidade oral (CAREY; PALOMO, 2008).

A osteonecrose de maxilares têm efeitos debilitantes sobre a integridade do osso maxilar com consequências estruturais e funcionais que prejudicam significativamente a qualidade de vida do paciente (BETH-TASDOGAN *et al.*, 2017; LEVEN; PRESTON, 2016; MALLYA; TETRADIS, 2018; MÂNEA *et al.*, 2018; RUGGIERO *et al.*, 2009; ZSÓFIA; ENIKŐ; ZSUZSANNA, 2018). Pode ser assintomática ou apresentar dor, edema, mobilidade dental, inchaço, dentes soltos e sensação de desconforto (RUGGIERO; FANTASIA; CARLSON, 2006).

A osteonecrose causada por medicamentos é definida clinicamente pela exposição do osso necrótico, mas também as seguintes características devem estar presentes, concomitantemente: i) paciente deve estar em tratamento ou ter sido submetido a tratamento prévio com agentes antirreabsortivos ou antiangiogênicos; ii) presença de osso exposto ou que pode ser sondado através de fístula intra e extraoral persistindo por mais de oito semanas; e iii) nenhum histórico de radioterapia ou lesão metastática evidente nos maxilares (RUGGIERO *et al.*, 2014).

O diagnóstico pode ser feito por exames de imagem, como a tomografia por emissão de pósitrons e a cintilografia, que podem ser úteis na detecção precoce de osteonecrose dos maxilares, permitindo ainda, quantificar o grau de lesão óssea. Os achados na tomografia computorizada se correlacionam com a apresentação clínica em 78,3% dos casos, concluindo que este exame de imagem apresenta uma capacidade razoável de detecção da osteonecrose de maxilares (ELAD; GOMORI; BEN-AMI, 2010; MIGLIORATI *et al.*, 2006).

A Associação Americana de Cirurgiões Dentistas, em 2013, propôs a utilização de um sistema de estadiamento da osteonecrose, para melhor orientar as diretrizes de tratamento e coletar dados para avaliar o prognósticos. O Quadro 1 demonstra a classificação sugerida por Ruggiero *et al.* (2014) sobre a osteonecrose maxilomandibular por uso de medicamentos dividida em quatro estágios clínicos (de 0 a 3), em ordem progressiva de acometimento.

Manifestações clínicas sem exposição óssea, como bolsa periodontal profunda, mobilidade dental, trismo, hipoestesia transitória ou dormência do lábio inferior e dor não odontogênica podem ser classificadas como osteonecrose de maxilares de estágio 0 (zero) ou não exposta (YONEDA *et al.*, 2017).

Quadro 1. Estágios clínicos da osteonecrose de maxilares

Estágios	Descrição
Estágio 0	Assintomático, osso não exposto com e alterações radiográficas presentes
Estágio 1	Osso necrótico exposto (sequestro) assintomático
Estágio 2	Osso necrótico exposto (sequestro) associado à dor e infecção
Estágio 3	Osso necrótico exposto (sequestro) em pacientes com dor, infecção e fratura patológica; fístula extra-oral; ou osteólise que se estende até a borda inferior da mandíbula ou assoalho da cavidade sinusal

Fonte: RUGGIERO SL, DODSON TB, FANTASIA J, GOODDAY R, AGHALOO T, MEHROTRA B, O'RYAN, F. American Association of Oral and Maxillofacial Surgeons position paper on medication-

related osteonecrosis of the jaw - 2014 update. *Journal of Oral and Maxillofacial Surgery*, v. 72, p. 1938–1956, 2014.

2.1.2 Diagnóstico diferencial da osteonecrose associada ao uso de medicamentos

O diagnóstico diferencial pode ser definido como uma hipótese formulada pelo profissional, tendo como base a sintomatologia apresentada pelo paciente durante o exame clínico. A partir dele, o profissional pode selecionar testes terapêuticos ou exames complementares específicos a fim de obter o diagnóstico final (RUGGIERO *et al.*, 2006).

A Sociedade Americana de Investigação Óssea e Mineral (*American Society for Bone and Mineral Research* - ASBMR) menciona que o diagnóstico diferencial de osteonecrose oral associada ao uso de medicamentos deve excluir as doenças intra-oraivas mais comuns, como doença periodontal, gengivite ou mucosite, osteomiolite infecciosa, disfunção temporomandibular, sinusite, patologia periapical por cárie dentária, osteoradionecrose, osteonecrose cavitária induzindo nevralgia e tumores ósseos ou metástases (KHOSLA *et al.*, 2007; RUGGIERO *et al.*, 2014).

Também deve-se excluir as doenças que apresentam exposição óssea sem história da utilização de bisfosfonatos como trauma, infecção por herpes Zoster associada a osteonecrose, sequestro benigno da tábua óssea lingual ou periodontite ulcerativa necrotizante associada ao HIV (*Human Immunodeficiency Virus* - Vírus da Imunodeficiência Humana) (KHOSLA *et al.*, 2007; RUGGIERO *et al.*, 2014).

2.2 Etiopatogênese da osteonecrose oral e o risco do uso dos bisfosfonatos

O processo fisiológico da remodelação óssea é estabelecido a partir do equilíbrio entre a deposição (atividade osteoblástica) e a reabsorção (atividade osteoclastica) desse tecido. Entretanto, o processo patológico se estabelece quando ocorre um desequilíbrio entre essas atividades (RUGGIERO *et al.*, 2014).

A colonização bacteriana está presente na osteonecrose. Como a cavidade oral está propensa a traumatismos devido à sua mucosa delgada e a uma microbiota abundante e diversificada, não é esclarecido se a causa da infecção exerce um papel primário ou secundário no desenvolvimento da lesão e, se ocorre inicialmente no osso ou nos tecidos moles (WOO *et al.*, 2006).

O uso de medicamentos antirreabsortivos e antiangiogênicos parece ser considerado o principal fator de risco para o desenvolvimento da osteneocrose cuja intensidade pode variar de acordo com o tipo, a dose, a via de administração e a duração da exposição ao medicamento (CLEZARDIN, 2013; HAMADEH; NGWA; GONG, 2015; RUGGIERO *et al.*, 2009; RUGGIERO *et al.*, 2014). Há também outras classes de medicamentos que podem causar diminuição da capacidade de remodelação óssea, tais como os quimioterápicos e corticoides (GOODELL, 2020).

Outros fatores de risco para a osteoneocrose são: sistêmicos (presença de diabetes *mellitus*, tabagismo e alcoolismo) (RUGGIERO *et al.*, 2014; MIGLIORATI *et al.*, 2005), demográficos (como idade e raça) e genéticos (polimorfismos de nucleotídeo único no gene do citocromo P450-2C [CYP2C8]) (ATFBROJ, 2007; CARVALHO *et al.*, 2018).

O estado geral do paciente, o grau de imunossupressão, a história de transplante de medula óssea ou de células estaminais, bem como fatores de risco locais (como estado de saúde oral e história de traumatismo local, cirurgia dento-alveolar ou infecção dentária) podem causar e/ou agravar o quadro da osteneocrose oral (ATFBROJ, 2007; CARVALHO *et al.*, 2018; DODSON, 2009; GOODELL, 2020).

2.3 Medicamentos antireabsortivos da classe dos bisfosfonatos

Os bisfosfonatos atuam como reguladores fisiológicos da calcificação e potentes inibidores específicos de reabsorção óssea mediada pelos osteoclastos. Eles são análogos sintéticos do pirofosfato, que se liga à hidroxiapatita encontrada no osso (RUGGIERO *et al.*, 2009; EID; ATLAS, 2014).

O mecanismo de ação dos bisfosfonatos ocorre a nível celular preferencialmente em locais de reabsorção óssea, especificamente sob os osteoclastos. Estas células aderem normalmente à superfície óssea porém, não apresentam a borda em escova, indicativa de reabsorção ativa. Estes medicamentos não interferem com o recrutamento ou fixação dos osteoclastos, mas inibem a atividade dos mesmos (FERREIRA JUNIOR *et al.*, 2007; EID; ATLAS, 2014).

Na cadeia R2 dos bisfosfonatos foi notada a presença de nitrogênio fazendo com que estes medicamentos sejam classificados em bisfosfonatos nitrogenados ou aminobisfosfonatos representados por pamidronato, alendronato, ibandronato, risedronato e zoledronato. Os bisfosfonatos não nitrogenados são o tidronato,

tiludronato e clodronato (FERREIRA JUNIOR *et al.*, 2007; RUSSEL *et al.*, 2007; CLEZARDIN, 2013).

O mecanismo de ação da osteonecrose causada pelos bisfosfonatos não é completamente compreendido, mas pressupõe-se que estes medicamentos causem obliteração dos vasos sanguíneos locais, produzindo uma necrose óssea avascular. Assim, a propriedade antiangiogênica dos bisfosfonatos combinada com outros medicamentos com esta mesma propriedade, ou à presença de comorbilidades (como diabetes *mellitus*) podem aumentar o risco de persistência e de progressão desta doença (RUGGIERO *et al.*, 2004).

Uma vez que os bisfosfonatos inibem a atividade osteoclástica, ocorre uma marcada supressão do metabolismo ósseo, comprometendo as propriedades biomecânicas dos maxilares e levando ao acúmulo de múltiplas microlesões. O osso cortical torna-se mais compacto, devido à contínua mineralização óssea pelos osteoblastos sem o contra balanço osteoclástico, elevando as chances de ocorrer futura fratura. Diante deste quadro, a ocorrência de traumatismo ou de infecção induz a necessidade de reparação óssea acima da capacidade de renovação do osso maxilar hipodinâmico, resultando assim em necrose óssea (WOO; HELLSTEIN; KALMAR, 2006).

Atualmente existem quatro gerações de bisfosfonatos disponíveis, conforme descrito no Quadro 2. Seu potencial de inibir a reabsorção óssea aumenta de uma geração para outra. Basicamente, o grupo de aminas aumenta exponencialmente a potência do fármaco e leva à supressão da regeneração óssea, com propriedades antiangiogênicas e ativadoras de linfócitos T, resultando em um efeito tumoricida ordenado (RUSSEL, 2007; CLEZARDIN, 2013). Quando utilizados como medicamentos, eles têm efeitos biológicos no metabolismo do cálcio, inibindo a calcificação e a reabsorção óssea (RUGGIERO *et al.*, 2009); com consequente ação no remodelamento ósseo e aumento da mineralização e da matriz óssea (BROZOSKI *et al.*, 2012; CVS, 2013; RUGGIERO *et al.*, 2014; SILVA *et al.*, 2016).

Os bisfosfonatos também são utilizados na indústria de cremes dentais para diminuir a formação de cálcio dental, por meio da inibição da precipitação do cálcio (RUGGIERO *et al.*, 2009).

Quadro 2. Medicamentos da classe dos bisfosfonatos disponíveis de acordo com a geração

Geração	Classificação	Nome genérico
Primeira geração	Não Nitrogenados	Etidronato
		Clodronato
Segunda geração	Nitrogenados Alquilaminos	Pamidronato
		Alendronato
Terceira geração		Neridronato
		Ibandronato
Quarta geração	Nitrogenados Heterocíclicos	Risendronato
		Zoledronato

Fonte: RUSSELL, R.G. Bisphosphonates: mode of action and pharmacology. *Journal of the American Academy of Pediatrics*, v. 119, n. 2, p. 150-162, 2007.

Os bisfosfonatos de uso oral são etidronato, tiludronato, alendronato, ibandronato e risendronato. Eles são utilizados na profilaxia e tratamento da hipercalcemia, doenças ósseas como a osteoporose, osteogênese imperfeita da infância e doença de *Paget* (BROZOSKI *et al.*, 2012; CARVALHO, 2018; CVS, 2013; RUGGIERO *et al.*, 2014; SILVA *et al.*, 2016) (Quadro 2).

No período de maio de 2003 a abril de 2004, estima-se que foram realizadas aproximadamente 22 milhões de prescrições de alendronato nos EUA, sendo considerado o bisfosfonato mais prescrito para o tratamento da osteoporose no mundo (ADA, 2006). Dados mais recentes a respeito das prescrições não foram encontrados, bem como dados de outros países.

Os bisfosfonatos intravenosos como o clodronato, pamidronato e zoledronato são utilizados no tratamento de hipercalcemia vinculada a malignidade, prevenção de metástases ósseas na mama, próstata e câncer do pulmão, controle de mieloma múltiplo e doença de *Paget* (BROZOSKI *et al.*, 2012; CARVALHO, 2018; CVS, 2013; RUGGIERO *et al.*, 2014; SILVA *et al.*, 2016) (Quadro 2).

Os bisfosfonatos tem absorção extremamente rápida no esqueleto. Cerca de 50% da sua dose administrada é absorvida em 30 minutos e mostra alta afinidade para áreas de rápido turnover ósseo (CARIOLATTO *et al.*, 2017).

A meia vida longa, estimada em 10 anos ou mais, ocorre especialmente para os bisfosfonatos que contém nitrogênio. Isto ocorre devido ao seu acúmulo dentro da rede de cristais de hidroxiapatita no osso. O processo para remover os bisfosfonatos

desse local ocorre pela ação dos osteoclastos, cujas células estão inibidas por estes medicamentos (HELLSTEIN, 2014; PAPAPOULOS; CREMERS, 2007).

A Associação Americana de Cirurgiões Orais e Maxilofaciais descreveu uma taxa de risco de desenvolver osteonecrose por terapêutica com bisfosfonato oral de cerca de 0,5% após procedimentos cirúrgicos dentários. O risco variou de 1,6 a 14,8% nos pacientes que receberam estes medicamentos por via intravenosa. Entretanto, tais informações foram baseadas em apenas dois estudos publicados no ano de 2012 (RUGGEIRO *et al.*, 2014).

Estudo de revisão reportou que pacientes com câncer que receberam bisfosfonatos por via endovenosa tiveram risco de 2,7 a 4,2 vezes maior de desenvolver osteonecrose de maxilares comparados aos pacientes que não utilizaram os bisfosfonatos (HAMADEH; NGWA; GONG, 2015). Isto também se deve ao fato de que a dose dos bisfosfonatos por via intravenosa em doentes oncológicos é até 12 vezes superiores à dose usada em condições como a osteoporose (WOO; HELLSTEIN; KALMAR, 2006).

No Brasil, os bisfosfonatos aprovados pela ANVISA são alendronato, clodronato, ibandronato, risedronato, pamidronato e zoledronato. Dentre eles, o alendronato, risedronato e pamidronato foram incorporados pelo Sistema Único de Saúde (MS, 2012).

Em 2004, o laboratório responsável pela introdução no mercado dos bisfosfonatos intravenosos, pamidronato e zoledronato, alertou os profissionais de saúde para os riscos associados ao desenvolvimento de osteonecrose dos maxilares. Este alerta foi suficiente para que em 2005, fossem incluídos todos os bisfosfonatos, inclusive as formas orais, como potentes desencadeadores dos processos de osteonecrose (CARVALHO *et al.*, 2008; ABUGHAZALEH; KAWAR, 2011).

A potência do fármaco também tem relação com o risco da osteonecrose. Se compararmos com o etidronato, o pamidronato é 100 vezes mais potente e o zoledronato é 10.000 vezes mais potente (Quadro 3). Desta maneira, o risco da osteonecrose é bem maior com fármacos que possuem maior potência (DURIE; KATZ; CROWLEY, 2005).

Quadro 3. Potencial antirreabsortivo dos bisfosfonatos destacados por geração

Grupos	Nome genérico	Via de administração	Potência
Não nitrogenados	Etidronato	Oral	1x
	Clodronato	Intravenoso	10x
	Tiludronato	Oral	10x
Nitrogenados alquilamino	Pamidronato	Intravenoso	100x
	Alendronato	Oral	500x
	Ibandronato	Oral/intravenoso	1.000x
Heterocíclicos	Risedronato	Oral	2.000x
	Zoledronato	Intravenoso	10.000x

Fonte: CARVALHO, LNV; DUARTE, NT; FIGUEIREDO, MA; ORTEGA, KL. Medication-Related Osteonecrosis of the Jaw: Diagnosis, treatment and prevention. *Revista CES Odontologia*, v. 31, n. 2, p. 48-63, 2018.

A Agência Europeia de Medicamentos (*European Medicines Agency - EMEA*), em 2009, elencou a osteonecrose como um dos assuntos prioritários para a pesquisa relacionada à segurança de medicamentos para o ano de 2010 (EMEA, 2010).

Uma boletim publicado na Europa, em 2009, sobre o risco de osteonecrose de mandíbula associada ao uso de bisfosfonatos teve o intuito de alertar os profissionais sobre este evento adverso e oferecer orientações sobre ações a serem tomadas pela Agência Reguladora de Medicamentos e Produtos de Saúde (*Medicines and Healthcare Products Regulatory Agency - MHRA*) do Reino Unido (MHRA, 2009).

Em 2013, a Agência Nacional de Vigilância Sanitária (Anvisa) também alertou para este evento adverso em um boletim que discutiu a eficácia e a segurança do tratamento da osteoporose com esta classe de medicamentos (BRATOS, 2013).

O Centro de Vigilância Sanitária da Secretaria Estadual de Saúde de São Paulo (CVS/SES/SP) analisou neste cenário 382 notificações de suspeitas de osteonecrose por medicamentos recebidas no período de maio de 2005 a agosto de 2013, por meio do sistema eletrônico de notificação – PERIweb. Foram identificadas 998 reações adversas graves ou clinicamente significativas envolvendo os medicamentos da classe dos bisfosfonatos. A osteonecrose de mandíbula representou 14% do total das reações graves, correspondendo a 56% das reações do sistema muscular ou esquelético. Outras reações incluíram fraturas, artralgia, mialgia e dor óssea (CVS, 2013).

2.4 Outros medicamentos com potencial de causar osteonecrose oral

O uso dos bisfosfonatos, juntamente com outros fármacos antirreabsortivos e antiangiogênicos, usados para o tratamento de câncer e osteoporose, aumentou rapidamente nos últimos 20 anos. Em 2014, a Associação Americana de Cirurgiões Maxilofaciais (*American Association of Maxillofacial Surgeons - AAOMS*) sugeriu o uso do termo osteonecrose de maxilares relacionada à medicação (*Medication-Related Osteonecrosis of the Jaw – MRONJ*) (GOODELL, 2020).

Os antiangiogênicos como o sunitinibe, lenalidomida e o sorafenibe são utilizados no tratamento de tumores gastrointestinais, carcinomas de células renais, tumores neuroendócrinos e outras malignidades. Esses medicamentos interferem na formação de novos vasos sanguíneos, ligando-se a várias moléculas de sinalização, interrompendo a cascata de sinalização da angiogênese (GOODELL, 2020; RUGGIERO *et al.*, 2014).

O denosumabe, um anticorpo monoclonal, inibe a função dos osteoclastos que é a principal célula que promove a reabsorção óssea. Esse medicamento, administrado por via subcutânea e a cada seis meses, diminui o risco de fratura vertebral e do quadril em pacientes com osteoporose. Também pode ser utilizado em doenças ósseas como tumores sólidos, porém não são indicados para o tratamento de mieloma múltiplo (PAPAPOULOS *et al.*, 2012; RUGGIERO *et al.*, 2014). Ao contrário dos bisfosfonatos, o denosunabe não se liga ao osso e seu efeito sobre a remodelação óssea é diminuído, principalmente dentro de seis meses após a interrupção do tratamento (RUGGIERO *et al.*, 2014).

O Quadro 4 descreve as características clínicas dos fármacos com risco de causar osteonecrose de maxilares.

Quadro 4. Características clínicas dos fármacos associadas à osteonecrose de maxilares

Classe farmacológica	Ano de aprovação pela FDA	Comercializado no Brasil	Nomes comerciais (laboratório)	Via de administração	Indicações
Bisfosfonatos não nitrogenados					
Etidronato	1997	Não	Didronel (Procter & Gamble)	Oral	Osteoporose e doença de <i>Paget</i>
Clodronato	Não aprovado no Canadá e Europa	Sim	Bonefós (Bayer) Ostac (Asta)	Intravenoso	Hipercalcemia vinculada a malignidade e mieloma múltiplo
Tiludronato	1997	Não	Skelid (Aventis)	Oral	Doença de <i>Paget</i>
Bisfosfonatos alquilaminos					
Pamidronato	1991	Sim	Aredia (Novartis)	Intravenoso	Hipercalcemia vinculada a malignidade; prevenção de metástases ósseas a partir da mama, próstata e câncer de pulmão; controle de mieloma múltiplo e doença de <i>Paget</i>
Alendronato	1995	Sim	Fosamax (Msd), Alendronato (Legrand, Biosintética, Sandoz, Germed, Nova Química, Brainfarma, Biolan Sanus), Bonalen (União Química), Minusorb (UCI Farma), Cleveron (Trb Pharma), Ostenan (Marjan), Bonagran (Legrand), Ostra T (Teuto), Ossomax (Globo), Alenost (Wyeth), Endrostan (Delta), Ostelox (Melcon), Boneprev (Sandoz), Osteoral (Aché), Osteoform (EMS), Alendil (Farmoquímica), Alendrus (Brainfarma), Alendósse (EMS), Endronax (Solvay Farm), Terost (Bio Ativus)	Oral	Osteoporose, doença de <i>Paget</i> e osteogenese imperfeita da infância
Ibandronato	2005	Sim	Boniva/Bonviva (Roche), Ibandronato de sódio (Aché)	Oral	Osteoporose
Bisfosfonatos nitrogenados					
Risedronato	1998	Sim	Actonel (Aventis), Osteotrat (Aché), Risedronato sódico (Prati, Donaduzzi, Biosintética, EMS, Sigma Pharma, Germed Legrand).	Oral	Osteoporose e doença de <i>Paget</i>

Zoledronato	2001	Sim	Zometa (Novartis), Ácido Zoledrônico (Eurofarma, TKS), Zolibbs (Libbs), Zobone (TKS), Blaztere (Dr. Reddy's), Aclasta (Novartis), Reclast (Novartis)	Intravenoso	Hipercalcemia vinculada a malignidade; prevenção de metástases ósseas a partir da mama, próstata e câncer do pulmão; controle de mieloma múltiplo, osteoporose e doença de Paget
Outro antirreabsortivo					
Denosumabe	2010	Sim	Prolia (Glaxo Smith Kline), Xgeva (Amgen)	Subcutâneo	Osteoporose, aumento da massa óssea nos tratamentos de câncer de próstata ou de mama; prevenção de metástase óssea de tumores sólidos e tumor ósseo de células gigantes
Outros antiangiogênicos					
Bevacizumabe	2004	Sim	Avastin (Roche)	Intravenoso	Câncer cólo-retal, pulmão, mama e rins metastático e câncer epitelial de ovário, tuba uterina e peritoneal
Sunitinibe	2006	Sim	Sutent (Pfizer)	Oral	Carcinoma de células renais avançado, tumores estromais gastrointestinais, tumores neuroendócrinos do pâncreas avançado
Lenalidomida	2005	Sim	Revlimid (Celgene)	Oral	Mieloma múltiplo, síndrome mielodisplásica, tratamento da reação hansônica do tipo eritematosa nodoso ou tipo II, úlcera aftosa e doença do enxerto contra hospedeiro

Fonte: CARVALHO LNV; DUARTE NT; FIGUEIREDO MA; ORTEGA KL. Medication-Related Osteonecrosis of the Jaw: Diagnosis, treatment and prevention.

Revista CES Odontología, v.31, n.2, p.48-63, 2018.

2.5 Osteonecrose oral em usuários de bisfosfonatos submetidos a procedimentos odontológicos

Revisão sistemática que inclui 4.106 participantes com osteonecrose oral identificou diferentes doenças sistêmicas e outros fatores de risco para este efeito adverso, sendo 14 de origem médica e 11 de risco odontológico. O estudo incluiu 102 séries de casos e estudos de coorte e relatam os principais fatores de risco para osteonecrose sendo eles: extração dental (n= 78 estudos), uso de corticoides (n= 62), quimioterapia (n= 51), doença periodontal (n= 30 estudos), diabetes mellitus (n= 28), tabagismo (n=27) e doenças cardiovasculares (n= 21). O estudo sugere que avaliar a saúde sistêmica e imunológica do paciente é primordial para determinar quais pacientes apresentam maior risco de desenvolver osteonecrose oral (MCGOWAN; MCGOWAN; IVANOVSKI, 2018).

Alguns estudos observacionais descreveram na população com osteonecrose, o papel do procedimento odontológico no aparecimento ou agravamento desta condição.

Estudo retrospectivo desenvolvido em Isparta na Turquia, entre os anos de 2007 e 2012, determinou as características de 88 pacientes que desenvolveram osteonecrose da mandíbula. A maioria dos pacientes (82,9%) usava o zoledronato intravenoso, com duração média de tratamento de 36 meses. A osteonecrose foi desenvolvida em média nos primeiros 5 meses do medicamento. Em torno de 90% dos pacientes tinham histórico de procedimentos cirúrgicos orais. Trauma por prótese dentária estava presente em dois pacientes (5,7%) e doença periodontal em um dos pacientes (2,9%) (AKSOY *et al.*, 2017).

Estudo observacional realizado no Reino Unido, no período de junho de 2009 a maio de 2011, descreveu 383 pacientes com osteonecrose oral devido ao uso de bisfosfonatos. Os bisfosfonatos foram administrados em 207 (56%) dos pacientes por via intravenosa, em 125 (34%) pacientes por via oral e em 27 (7%) deles foi usada a via oral e a intravenosa. O principal fator de risco para a osteonecrose foi a extração dentária (73% dos casos), sendo a mandíbula mais comumente afetada comparada a maxila (ROGERS *et al.*, 2014).

Estudo observacional coletou dados de quatro clínicas de cirurgia oral e maxilofacial em Skåne na Suécia, no período de janeiro de 2012 a dezembro de 2015. A incidência de osteonecrose em pacientes que usaram bisfosfonatos orais foi de

0,04% e de 1,03% em pacientes que usavam bisfosfonatos intravenosos. A extração dental foi o procedimento odontológico mais comum presente nos pacientes que desenvolveram a doença oral (HALLMER *et al.*, 2018).

Estudo de coorte de dados de um sistema nacional de seguro saúde em Taiwan, realizado no período de 2000-2010, verificou que pacientes com osteoporose em tratamento com bisfosfonatos tiveram risco 2 vezes maior (intervalo de confiança de 95% - IC 95%: 1,58 - 2,65) de ter osteonecrose comparado aos pacientes com ausência de osteoporose. Além disso, um efeito cumulativo da frequência de extração dentária aumentou o risco de osteonecrose, de acordo com a gravidade da osteoporose (HUANG *et al.*, 2015).

A cirurgia dento alveolar é considerada uma intervenção odontológica invasiva, que pode traumatizar os tecidos duros e moles. Quando ocorre intervenção cirúrgica, é necessária a reparação tecidual para que haja a recuperação dos tecidos lesados. Então, esta intervenção pode ser considerada como um importante fator de risco para desenvolver osteonecrose de maxilares em usuários de antirreabsortivos. Alguns estudos têm reportado que em pacientes com osteonecrose, a extração dental foi considerada evento que precipitou a manifestação da doença, com uma taxa de 52 a 61% dos pacientes diagnosticados (VAHTSEVANOS *et al.*, 2009; SAAD *et al.*, 2012; FEHM *et al.*, 2009).

Overview de revisões sistemáticas avaliou o risco de falha no implante dentário ou perda óssea marginal em pacientes em tratamento com bisfosfonatos. Os autores não observaram maior risco de falha com os pacientes que usaram bisfosfonatos comparados aos que não usaram bisfosfonatos. Pacientes que usavam bisfosfonatos e foram submetidos a trauma cirúrgico durante a instalação de implantes dentários foram mais suscetíveis a osteonecrose de maxilares. Entretanto, devido divergências na descrição dos resultados das revisões sistemáticas, autores concluem que se faz necessário mais estudos primários individualizando o efeito de diferentes tipos de bisfosfonatos e vias de administração para avaliar o seu real impacto no desempenho de implantes dentários (MENDES *et al.*, 2018).

2.6 Prevenção e tratamento da osteonecrose de maxilares

A prevenção é considerada muito importante para evitar a intercorrência da osteonecrose. Recomenda-se que os pacientes sejam submetidos a avaliações dentárias e recebam o tratamento odontológico necessário antes de iniciar a terapia com bisfosfonato (ATFBROJ, 2007; GOODELL, 2020; RUGGIERO *et al.*, 2014).

Estudo retrospectivo, coletou dados de 273 pacientes com osteonecrose, atendidos no serviço odontológico *Memorial Sloan Kettering Cancer Center* (Nova York), entre 1998 e 2016. Os autores investigaram a relação entre o medicamento e a osteonecrose e o papel da avaliação odontológica pré-medicação na prevenção da doença. Os pacientes foram classificados em dois grupos: i) avaliação odontológica pré-medicação (de antirreabsortivos e/ou antiangiogênicos) e ii) avaliação após exposição prévia a estes medicamentos. Pacientes em uso de denosumabe desenvolveram osteonecrose mais cedo em comparação ao zoledronato e pamidronato. O grupo submetido a procedimento odontológico previamente ao uso dos medicamentos teve menor incidência de osteonecrose (0,9%) em comparação ao grupo que recebeu intervenção odontológica após a terapia medicamentosa (10,5%) (OWOSHO *et al.*, 2018).

Há um exame laboratorial de dosagem do marcador específico da reabsorção óssea, Telopeptídeo-C Terminal do colágeno tipo I (*Type I Collagen Terminal C-Telopeptide - CTX*), liberado durante a remodelação e renovação óssea (RUGGIERO *et al.*, 2014). Embora esse marcador esteja disponível no mercado há mais de uma década, ele foi subutilizado no cenário clínico, pois sua eficácia na orientação das decisões clínicas é limitada (YOON; RUBINOVA; ISLAM, 2018).

O CTX estará aumentado em pacientes com doença de *Paget*, osteoporose, osteomalácia, osteodistrofia renal, hiperparatireoidismo e hipertireoidismo e, ainda, em uso de glicocorticoides. Este é um exame de alta sensibilidade, mas de baixa especificidade (MARX; CILLO; ULLOA, 2007).

O uso de bisfosfonatos diminui as taxas de CTX após 3 meses de tratamento, o que nos leva a acreditar que a diminuição dos níveis séricos deste marcador possa indicar risco para a realização das intervenções cirúrgicas. Os valores laboratoriais normais de CTX são de 300-600 pg/mL. Valores entre 100 e 150 pg/mL indicam risco moderado, valores acima de 150 pg/mL representam baixo risco e menores do que

100 pg/mL indicam para um alto risco de osteonecrose (AAOMS, 2007; RUGGIERO *et al.*, 2014).

Em relação à osteonecrose oral, sabe-se que quanto melhor a condição de higiene bucal do paciente a ser submetido ao tratamento cirúrgico, mais favorável é o prognóstico. Na maioria das vezes, nem o paciente e nem o médico conhecem as possíveis repercussões orais que essa classe de medicamentos pode representar, afetando significativamente a qualidade de vida dos mesmos (MALLYA; TETRADIS, 2018).

As abordagens para o tratamento devem incluir educação e conscientização do paciente, visitas regulares ao dentista para reavaliação e preservação do quadro clínico, eliminação dos hábitos relacionados a tabagismo e ingestão alcóolica, cuidados de rotina de higiene bucal para reduzir o risco de cárie e doença periodontal, uso de antibióticos e antimicrobianos (TONG; HO; WONG, 2010).

Uma vez que a lesão ocorre, o cirurgião-dentista deve usar algumas medidas para tentar tratar e impedir a progressão da doença. Isto significa utilizar de meios como antibioticoterapia, enxaguatório bucal com gluconato de clorexidina 0,12%, tratamento da remissão de dor, desbridamento ósseo quando necessário e prevenção de infecção, bem como manter-se atento às novas opções de tratamento eficazes que podem surgir no decorrer dos anos (RUGGIERO *et al.*, 2014).

O objetivo do tratamento da osteonecrose é aliviar a dor, controlar a infecção e estabilizar a progressão da exposição óssea (GUPTA; GUPTA, 2018). Dependendo do estágio da doença, podem ocorrer tratamentos conservadores, como lavagem com anti-sépticos e antibióticos orais; e cirurgias minimamente invasivas, como sequestrectomia ou desbridamento. Em alguns casos, ambos os tratamentos devem ser considerados (COROPCIUC *et al.*, 2017).

O Quadro 5 descreve as técnicas utilizadas para o tratamento da osteonecrose oral, descritas por estudos publicados nos últimos 11 anos. Observa-se que o uso dos antibióticos foi o procedimento mais utilizado, seguido do uso de plasma rico em plaquetas. A terapia com laser de baixa potência foi apresentada como uma abordagem mais recomendada quando combinada com antibioticoterapia e desbridamento ósseo. A oxigenação hiperbárica apresentou resultados importantes com taxas de sucesso que variaram entre 25% e 90% (RIBEIRO *et al.*, 2018).

Revisão sistemática avaliou, por meio de ensaios clínicos controlados randomizados, os efeitos das intervenções não cirúrgicas e cirúrgicas (únicas ou

combinadas) em relação a nenhum tratamento, placebo ou controle ativo para tratamento de pacientes com osteonecrose maxilares induzida por medicamentos.

Quando a osteonecrose oral está instalada, o tipo de tratamento a ser efetuado dependerá da fase da doença e tem como objetivo o alívio da dor, o controle da infecção instalada e estabilização da progressão da exposição óssea (OTTO *et al.*, 2009). Na fase inicial, tratamento mais conservador é indicado e inclui lavagens com antissépticos orais, juntamente com a utilização de antibióticos. Em fases mais avançadas, o tratamento de escolha são cirurgias minimamente invasivas como a sequestrectomia ou desbridamento. Em alguns casos, ambos os tratamentos devem ser considerados. Em geral, as evidências disponíveis não são suficientes para provar ou refutar o benefício dos tratamentos conservadores ou cirúrgicos usadas no tratamento destes pacientes (BETH-TASDOGAN *et al.*, 2017).

Quadro 5. Abordagens de tratamento para osteonecrose oral descritas na literatura

Referências	Pacientes (N)	Técnica tratamento positivo	Proservação (meses)
Agrillo <i>et al.</i> , 2012	94	ATB, DNC, O	6,5 (média)
Curi <i>et al.</i> , 2011	25	ATB, C, PRP	36 (média)
Freiberger <i>et al.</i> , 2012	25	ATB, C, HBO	24
Klingelhöffer <i>et al.</i> , 2016	76	ATB, C	6-24
Martins <i>et al.</i> , 2012	22	ATB	6
Melea <i>et al.</i> , 2014	38	ATB, DNC, C, PRP, TLBI	6 (mínimo)
Minamisako <i>et al.</i> , 2016	01	ATB, DNC, TLBI, TFD	12
Ripamonti <i>et al.</i> , 2011	10	ATB, DNC, O	8
Rugani <i>et al.</i> , 2015	38	ATB, C	12
Schubert <i>et al.</i> , 2012	54	C	9
Thumbigere-Math <i>et al.</i> 2009	26	ATB, HBO, C	6 (mínimo)
Vescovi <i>et al.</i> 2014	192	DNC	6-50

ATB: Antibioticoterapia; C: Cirurgia; HBO: Oxigenação hiperbárica; DNC: Debridamento não cirúrgico; O: Óleo ozonizado; Pento, Pentoxifilina e Tocoferol; PRP: Plasma rico em plaquetas; TFD: Terapia fotodinâmica; TLBI: Terapia a laser de baixa intensidade.

Fonte: RIBEIRO GH; CHRUN ES; DUTRA KL; DANIEL FI; GRANDO JL. Osteonecrosis of the jaws: a review and update in etiology and treatment. **Revista Brasileira de Otorrinolaringologia**, v. 84, n. 1, p.102-108, 2018.

Quanto melhor a condição oral do paciente a ser submetido ao tratamento com bisfosfonatos, mais favorável é o prognóstico da doença. No entanto, a maioria dos médicos, cirurgiões dentistas e o paciente desconhecem as possíveis repercussões orais que essa classe de medicamentos pode causar (RUGGIERO *et al.*, 2014).

A CVS/SES-SP, em 2013, elaborou um documento com recomendações aos prescritores, cirurgiões dentistas e pacientes alertando sobre o risco de osteonecrose em maxilares associado ao uso de bisfosfonatos, a fim de evitar exposição desnecessária ao medicamento, descritas no (Quadro 6).

Uma estudo de coorte analisou os benefícios da descontinuação do uso bisfosfonatos em evitar a osteonecrose oral. O estudo reportou resultados de dois grupos de pacientes que necessitavam de extrações dentais divididos em: pacientes que não interromperam o uso do bisfosfonato ($n=179$ pacientes) e o grupo que descontinuou o uso destes medicamentos ($n=286$ pacientes). Um paciente do grupo que continuou o uso dos bisfosfonatos desenvolveu osteonecrose. Os pacientes do grupo descontinuaram a terapia com bisfosfonato em média de 39 meses antes da extração dental. O estudo conclui que a descontinuação dos bisfosfonatos por vários meses antes do procedimento de extração pode ser considerada, entretanto, alerta para o fato de que as evidências ainda são limitadas (KANG; PARK; KIM, 2020).

Quadro 6. Recomendações aos prescritores, cirurgiões dentistas e pacientes sobre os cuidados na administração de bisfosfonatos

Aos prescritores
<ul style="list-style-type: none"> • O emprego de fármacos para a doença osteoporose deve ser reservado a pacientes com a doença confirmada e alto risco para fratura. Nos demais casos, deve-se prevenir a doença por meio da prática de exercícios físicos, adoção de medidas para a prevenção da queda, dieta e sua complementação com cálcio e vitamina D.
<ul style="list-style-type: none"> • O uso dos bisfosfonatos está contraindicado nos seguintes casos: hipersensibilidade ao medicamento, acalasia e estenose esofágica, impossibilidade de o paciente se manter em pé ou sentado por 30 minutos (para uso oral), função renal comprometida com depuração da creatinina endógena abaixo de 35 ml/min e hipocalcemia (deve ser corrigida antes do início do tratamento).
<ul style="list-style-type: none"> • Deve-se ter cautela ao tratar pacientes com histórico de hipoparatiroidismo, risco de hipocalcemia ou grandes problemas gastrintestinais com bisfosfonatos.
<ul style="list-style-type: none"> • O medicamento deve ser tomado em jejum de 2 horas e ao menos 30 minutos antes da próxima refeição. Não deve ser tomado com outros medicamentos, inclusive carbonato de cálcio.
<ul style="list-style-type: none"> • Fatores de risco que devem ser considerados na prescrição são: potência do medicamento (o ácido zoledrônico é o mais potente), via de administração (maior risco para via endovenosa), acúmulo de dose, tratamentos concomitantes (em especial glicocorticoides), tabagismo e comorbidades.
<ul style="list-style-type: none"> • Um histórico de doenças odontológicas, procedimentos invasivos ou traumas nos dentes está associado a um aumento do risco de osteonecrose de maxilares.
<ul style="list-style-type: none"> • Deve-se ponderar, para cada paciente, se o uso de bisfosfonatos por mais de três anos é necessário e justificável.
Aos cirurgiões-dentistas
<ul style="list-style-type: none"> • Considere a possibilidade de osteonecrose de maxilares como um evento adverso associado ao uso de bisfosfonatos (alendronato, ácido clodrônico, ibandronato, risedronato, pamidronato e ácido zoledrônico). Na presença de dor ou suspeita de necrose na região mandibular, investigue o uso destes medicamentos e entre em contato com o prescritor.
Aos pacientes em uso de bisfosfonatos
<ul style="list-style-type: none"> • Realize uma avaliação odontológica antes do início do uso do bisfosfonato. Durante o tratamento, mantenha uma boa higiene bucal, acompanhamento odontológico e avise seu médico ou dentista em caso de qualquer dor, inchaço ou outro sintoma bucal.

FONTE: NÚCLEO DE FARMACOVIGILÂNCIA DO CENTRO DE VIGILÂNCIA SANITÁRIA DA SECRETARIA DE ESTADO DA SAÚDE DE SÃO PAULO (CVS), **Alerta Terapêutica em Farmacovigilância**, 2013.

3 OBJETIVOS

3.1 Objetivo Primário

Determinar o risco da osteonecrose de maxilares em usuários de bisfosfonatos submetidos a intervenção cirúrgica odontológica ou devido à trauma por prótese dentária, por meio de revisão sistemática e meta-análise.

3.2 Objetivos Secundários

Determinar o risco da osteonecrose oral em função da intervenção odontológica, do bisfosfonato prescrito, bem como a via de administração e sua indicação;

Determinar se há aumento no risco de osteonecrose oral em relação ao tempo de tratamento com bisfosfonatos;

Identificar lacunas nas evidências atuais e fazer recomendações para pesquisas futuras.

4 RESULTADOS

O artigo foi submetido em periódico ao periódico *international journal of oral and maxillofacial surgery*, seguindo as regras do Programa de Pós-graduação em Ciências Farmacêuticas (ANEXO 1).

Abaixo segue o comprovante de submissão.

Submission Confirmation for Risk of osteonecrosis in bisphosphonate users submitted to dental procedures: Systematic Review and Meta-Analysis

1 mensagem

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4.1 Title: Risk of osteonecrosis in bisphosphonate users submitted to dental procedures: systematic review and meta-analysis

Title: Risk of osteonecrosis in bisphosphonate users submitted to dental procedures: Systematic Review and Meta-Analysis

Short title: Oral osteonecrosis in bisphosphonate users and submitted to dental procedures

Lucio Henrique Ives Martins¹

Delaine Cristina Ferreira¹

Marcus Tolentino Silva¹

Rogério Heládio Lopes Motta²

Reginaldo Tavares Franquez¹

Cristiane de Cássia Bergamaschi^{1*}

Author affiliations

¹Graduate Program in Pharmaceutical Sciences, University of Sorocaba, Sorocaba, State of São Paulo, Brazil.

²Division of Pharmacology, Anesthesiology and Therapeutics, Faculdade São Leopoldo Mandic, Instituto de Pesquisas São Leopoldo Mandic, Campinas, Brazil.

Conflict of interest: The authors declare no conflict of interest.

***Corresponding author:**

Cristiane de Cássia Bergamaschi

cristiane.motta@prof.uniso.br

<https://orcid.org/0000-0002-6608-1806>

University of Sorocaba – UNISO. Rodovia Raposo Tavares, Km 92.5, 18023-000, Sorocaba, SP, Brasil. Phone/Fax: 55 15 2101 7104.

ABSTRACT

Although maxillary osteonecrosis be considered a rare condition, it can be refractory to available treatment therapies and clinically difficult to manage. Some dental procedures can represent risk factor for triggering the condition. No recent data on the risk of this adverse effect after dental interventions in bisphosphonate users were found in the literature. This study determined the risk of osteonecrosis of the jaw in bisphosphonate users undergoing dental interventions. This systematic review searched the following information sources: MEDLINE (via Ovid), EMBASE (via Ovid), Web of Science, Scopus, Virtual Health Library and Thesis Bank of the Coordination for the Improvement of Higher Education Personnel, with no restriction on language or publication date. Reviewers, in pairs and independently, selected the studies, extracted their data and assessed risk of bias. The risk of osteonecrosis in relation to bisphosphonate treatment duration was determined. The meta-analyses were pooled using the DerSimonian and Laird random effects model. A total of 27 studies (4,865 adult's patients) were included, with samples comprising predominantly females and older adults. The most used bisphosphonates were zoledronate by the intravenous route ($n= 17$ studies) and alendronate by the oral route ($n= 19$) for treating cancers ($n= 11$) or osteoporosis ($n= 16$), respectively. Dental extraction was the most common procedure ($n= 21$). Most of the studies were of low methodological quality ($n= 21$). The risk of osteonecrosis was 0.8% (95%CI: 0.5-1.2%) proving higher for intravenous bisphosphonate [8.9% (95% CI: 6.5 to 11.5%)] than orall [0.0% (0.0-0.1%)]. There was no association between longer treatment duration and greater risk of osteonecrosis. There is higher risk of oral osteonecrosis in intravenous bisphosphonate users submitted to dental extraction. Further studies collecting more detailed information on the bisphosphonates used and with greater methodological rigor are warranted. The present findings can help inform prescribers, dental surgeons and other health professionals on the risks of bisphosphonate use in patients undergoing dental interventions.

PROSPERO: CRD42020175480

Key-words: Osteonecrosis. Bisphosphonates. Jaw. Systematic review.

BACKGROUND

Bisphosphonates decrease bone resorption by acting directly on osteoclastic activity as synthetic pyrophosphate analogues, they bind to bone hydroxyapatite. These drugs have been used since the 1960s for the treatment of bone metastases, lung cancer, multiple myeloma, Paget's disease, metabolic metabolism disease control, among others; mainly for treatment and prevention of osteoporosis and osteopenia (BROZOSKI *et al.*, 2012; ALLEN *et al.*, 2016).

Oral osteonecrosis induced by bisphosphonates was first reported in 2003, when mandibular or maxillary bone lesions were demonstrated in patients using pamidronate or zoledronate, and characterized as injuries caused by a serious unknown adverse effect (MARX, 2003).

This condition is considered a sporadic complication associated with bisphosphonate therapy (CHIU *et al.*, 2018; DE ANTONI *et al.*, 2018; RUGGIERO *et al.*, 2009) leading to a significant debilitating impact on patients, decreasing their quality of life (BETH-TASDOGAN *et al.*, 2017; HUTCHENSON *et al.*, 2014; LEVEN; PRESTON, 2016; MALLYA; TETRADIS, 2018; MÂNEA *et al.*, 2018; RUGGIERO *et al.*, 2009; ZSÓFIA; ENIKŐ; ZSUZSANNA, 2018).

Clinically, these patients present areas of necrotic bone exposure of varying size, ranging from millimeters to larger areas, and which may remain asymptomatic. Lesions are usually associated with pain at the bone exposure site, dental mobility unrelated to periodontal diseases, trauma or other injuries, volume increase, presence of erythema, ulceration and sinus fistula hampering dental intervention (BROZOSKI *et al.*, 2012).

The goal of osteonecrosis treatment is to provide pain relief, control infection and arrest the progression of bone exposure (GUPTA; GUPTA, 2018). Depending on disease stage, conservative treatments such as washing with oral antiseptics and antibiotics, and minimally-invasive surgery such as sequestrectomy or debridement can also be performed. In some cases, both treatments must be considered (COROPCIUC *et al.*, 2017). Systematic review showed that the available evidence is yet insufficient to prove or refute the benefit of interventions used for treatment of this patient group (BETH-TASDOGAN *et al.*, 2017).

A growing number of cases of bisphosphonate-induced oral osteonecrosis are being reported in the scientific literature (BETH-TASDOGAN *et al.*, 2017; BROZOSKI

et al., 2012; DODSON, 2015; DI FEDE *et al.*, 2018; RASMUSSEN; ABTAHI, 2014; RIBEIRO *et al.*, 2018; RUGGIERO *et al.*, 2014).

Systematic review determined the risk of occurrence of osteonecrosis of the jaw related to the use of anti-resorptive medication to treat osteoporosis or oncological diseases (GAUDIN *et al.*, 2015). However, this information needs updating and the study was restricted to tooth extraction and failed to address other invasive procedures.

The current research question was “What is the risk of oral osteonecrosis in bisphosphonate users submitted to dental procedure?” Therefore, the present systematic review sought to determine the risk of osteonecrosis of the jaw in bisphosphonate users submitted to dental interventions.

METHODS

Protocol and registration

This systematic review adhered to the protocol defined by the Cochrane Handbook for Systematic Reviews of Interventions (HIGGINS *et al.*, 2011). The assessment was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (MOHER *et al.*, 2009) (Appendix A).

The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO), under protocol (CRD42020175480).

Eligibility criteria

Inclusion criteria

Population: individuals over 18 years submitted to dental surgery or that had trauma due to the use of a dental prosthesis receiving bisphosphonate therapy, regardless of route of administration. The bisphosphonates studied were: alendronate, clodronate, etidronate, ibandronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate and zoledronate.

Study types: randomized clinical trials (RCT) and observational studies (cohort, case-control, cross-sectional studies and case series) were included. Comparator groups for RCT and cohort studies were no dental intervention, other dental intervention or other type of intervention.

Exclusion criteria

Studies in which the whole population used combination therapy with chemotherapy or radiotherapy or other anti-resorptive drugs were excluded.

Outcomes evaluated

Risk of osteonecrosis of the jaw described in relation to dental procedure, route of administration of bisphosphonate, bisphosphonate used and indication of the use of bisphosphonate.

Literature search

Search for studies in electronic databases and metabusers

The searches were carried out on the following databases: MEDLINE (Ovid), EMBASE (Ovid), Web of Science, Scopus, Virtual Health Library and Thesis Bank of the Coordination for the Improvement of Higher Education Personnel (CAPES), without restrictions on language or year of publication. A search was carried out to identify all relevant publications up to July of 2020.

Searching other sources of queries in gray literature databases and other bibliographic search sources

Grey literature was searched using OpenGrey (<http://www.opengrey.eu/search/>) and the Grey Literature Report (<https://www.greylit.org/>).

Two reviewers (LHIM and DCF) analyzed the list of references or citations found in secondary studies to identify potentially eligible studies. The main authors of studies were contacted to obtain further information when needed.

Search Strategy

The search strategy was based on the National Library of Medicine's Medical Subject Headings (MeSH) and synonyms. In Chart 1 was shown the strategy executed on MEDLINE (via PubMed). The search strategies employed are given in Appendix B.

Chart 1. Search strategy for MEDLINE (via PubMed).

(“Osteonecroses” [Mesh] OR “Bone Necrosis” [Mesh] OR “Bone Necroses [Mesh] OR“ Necroses, Bone ”[Mesh] OR“ Necrosis, Bone ”OR“ Necrosis, Avascular, of Bone ”[Mesh] OR “Avascular Necrosis of Bone” [Mesh] OR “Bone Avascular Necrosis” [Mesh] OR “Necrosis, Aseptic, of Bone” [Mesh] OR “Aseptic Necrosis of Bone” [Mesh] OR “Bone Aseptic Necrosis” [Mesh] AND “Bisphosphonate Associated Osteonecrosis of the Jaw” [Mesh] OR “Bisphosphonate-Induced Osteonecrosis of the Jaw” [Mesh] OR “Bisphosphonate-Induced Osteonecrosis of the Jaw” [Mesh] OR “Bisphosphonate-Induced Osteonecrosis of the Jaws” Mesh “Bisphosphonate Induced Osteonecrosis of the Jaws” [Mesh] OR “Bisphosphonate-Related Osteonecrosis of the Jaw” [Mesh] OR “Bisphosphonate Related Osteonecrosis of the Jaw” [Mesh] OR “Osteonecrosis of the Jaws, Bisphosphonate-Associated” [Mesh] OR “Osteonecrosis of the Jaws, Bisphosphonate Associated” [Mesh] OR “Osteonecrosis of the Jaw, Bisphosphonate-Related ”[Mesh] OR“ Osteonecrosis of the Jaws, Bisphosphonate-Related ”[Mesh] OR “Osteonecrosis of the Jaws, Bisphosphonate Related” [Mesh] OR “Osteonecrosis of the Jaw, Bisphosphonate-Associated” [Mesh] OR “Osteonecrosis of the Jaw, Bisphosphonate Associated” [Mesh] OR “Bisphosphonate-Associated Osteonecrosis of the Jaws ”[Mesh] OR“ Bisphosphonate Associated Osteonecrosis of the Jaws ”[Mesh] OR“ Osteonecrosis of the Jaw, Bisphosphonate-Induced ”[Mesh] OR“ Osteonecrosis of the Jaw, Bisphosphonate Induced ”[Mesh] OR“ Bisphosphonate-Associated Osteonecrosis ” [Mesh] OR “Bisphosphonate-Associated Osteonecroses” [Mesh] OR “Osteonecroses, Bisphosphonate-Associated” [Mesh] OR “Osteonecrosis, Bisphosphonate-Associated” [Me sh] OR “Bisphosphonate Osteonecrosis” [Mesh] OR “Bisphosphonate Osteonecroses” [Mesh] OR “Osteonecroses, Bisphosphonate” [Mesh] OR “Osteonecrosis, Bisphosphonate” [Mesh] OR “Osteonecrosis of the Jaws, Bisphosphonate-Mesh] AND “Prevalence” [Mesh] OR “Prevalences” [Mesh]).

Studies selection

Determination of eligibility

Pairs of reviewers (LHIM, DCF and LHIM, RF) independently assessed potentially relevant titles and abstracts according to eligibility criteria.

A full list of potentially eligible articles was thus obtained. A selection form of studies was formulated and pre-texted. Before starting data extraction, calibration exercises were performed to ensure consistency among the reviewers.

The same reviewers independently evaluated the eligibility of each full text and resolved disagreements by consensus. A third reviewer (CCB) assisted in final decisions when necessary.

Data extraction

Pairs of reviewers (LHIM, DCF and LHIM, CCB), independently, extracted data from the studies included using a pre-typed data extraction form with instructions.

The reviewers performed the extraction of at least 2 articles to ensure consistency across them. Disagreements were resolved by consensus or by a third reviewer when necessary. We contacted study authors to resolve any uncertainties.

The main data extracted were related to participants (age, sex, and health problem), studies (study design, year of publication, and host country and institution venue), bisphosphonate used, dental procedure, measured outcomes and risk of bias.

Risk of bias

The quality of studies was assessed using an adapted tool standardized by Loney *et al.* (1998) in which the following criteria were evaluated: i) adequate sampling method, ii) description of sampling sources, iii) adequate sample size (when applicable), iv) adequate measurement of outcome (clear description of diagnostic criteria used), v) outcome measurement by non-biased evaluators (calibrated evaluators), vi) adequate response rate and description of refusals (refusal and loss up to 70%), vii) description of results (frequency data with confidence interval and analysis by sub-groups), and viii) description of study subject and similar to the question of interest.

For each criterion, "yes", "no" or "not applicable" was attributed. One point was assigned for each positive response. Studies were rated as high (7-8 points), moderate (4-6 points) or low (0-3 points) quality (MOREIRA *et al.*, 2019).

The risk of bias assessment was carried out by two reviewers (CCB and LHIM) and any differences were resolved by consensus.

Data synthesis

A descriptive summary was performed to present the results. Quantitative variables were expressed as mean and standard deviation, while categorical variables were expressed as numbers and proportions.

Meta-analyses were performed by pooling prevalences and incidences using the DerSimonian and Laird random effects model and the double arcsine transformation devised by Freeman-Tukey to stabilize the variances.

Heterogeneity was investigated by calculating the inverse of variance in a fixed-effect model, presented as percentage of I^2 (ABDALRAHMAN *et al.*, 2015). Heterogeneity was classified as low (0 to 25%), moderate (50%) or high (75%) (HIGGINS *et al.*, 2003).

Subgroup analyses were performed with information on the risk of osteonecrosis for dental procedure (dental extraction vs implant), main bisphosphonates used (alendronate vs zoledronate) and main clinical use of bisphosphonates (osteoporosis vs cancer).

The duration of treatment with bisphosphonates in relation to the risk of osteonecrosis was investigated by meta-regression of the prevalences or incidences identified in double arcsine, in the moment model with the maximum likelihood restricted with the modification of the variance of the coefficients suggested by Knapp and Hartung (KNAPP; HARTUNG, 2003).

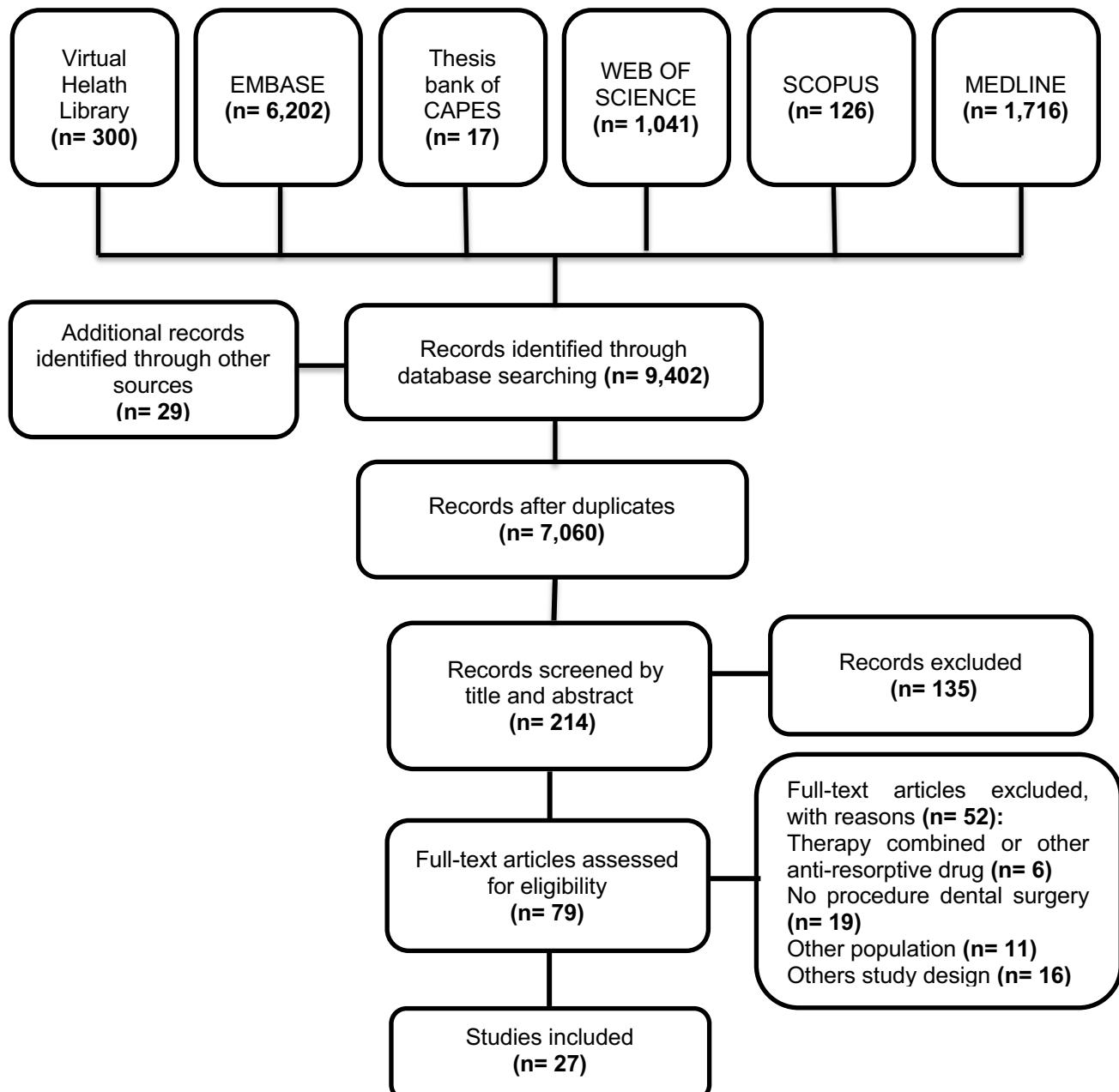
The publication bias was assessed by visual inspection of funnel plots. In all analyses, 95% confidence intervals (95% CI) were used. The analyses were performed using the statistical software STATA® version 14.2 (Stata Corp, College Station, United States).

5 RESULTS

Literature search results

Of a total of 9,402 articles retrieved (2,345 duplicates), 79 were considered potentially eligible and 27 of these articles were included in the study (Figure 1). List of excluded studies is described in Appendix C.

Figure 1. Flowchart of the included studies.



Description of included studies (Table 1)

A total of 10 cohort studies (HASEGAWA *et al.*, 2013; HUTCHESON *et al.*, 2014; KANG *et al.*, 2020; KOKA *et al.*, 2010; MIGLIORATI *et al.*, 2013; SEDGHIZADEH *et al.*, 2009; SIEBERT *et al.*, 2013; SHUDO *et al.*, 2018; VAHTSEVANOS *et al.*, 2009; YAMAZAKI *et al.*, 2012), 2 RCTs (MOZZATI; ARATA; GALLESIO, 2012 and MOZZATI; ARATA; GALLESIO, 2013), 2 cross-sectional study (GRANT *et al.*, 2008; ALZOMAn, 2011) and 13 case series (FERLITO *et al.*, 2011; FUGAZZOTTO *et al.*, 2007; LAZAROVICI *et al.*, 2010; LODI *et al.*, 2010; O'CONNELL *et al.*, 2013; OTTO *et al.*, 2015; SAIA *et al.*, 2010; SANCHIS *et al.*, 2014; SHABESTARI *et al.*, 2010; SCOLETTA *et al.*, 2011; SCOLETTA *et al.*, 2013, VESCOVI *et al.*, 2013 and ZAHID *et al.*, 2011) were included in this review. The studies were published between 2008 and 2020 and carried out mostly at teaching institutions mainly in Europe. Data collection was performed between 1998 and 2017.

The 27 studies included a total of 4,865 participants. The majority of participants were female and aged between 63.8 and 73.0 years. The main reasons for use of bisphosphonates were due to cancers (n= 11) and osteoporosis (n= 15).

The most common dental procedure described was dental extraction (n= 22) and 6 studies included information on implant.

Most commonly used bisphosphonates were alendronate (n= 19) and zoledronate (n= 16). In 17 studies, the patients used different bisphosphonates.

Regarding route of administration, 10 studies described the oral route only, whereas 8 studies described the intravenous route. Dental extraction was the most common procedure for patients who used oral bisphosphonates (n= 7) or intravenous bisphosphonates (n= 9). In general, the studies did not report the dose or the posology prescribed and the duration of use of each drug was also not reported (Table 2).

Table 1. Characteristics of included studies (n= 27 studies, 4,865 population)

Variables/ Author (year)	Study design	City/ country	Data collection period	Total population/ Female (%)	Age (years) mean ± sd or median (min- max)	Dental Procedure/ Prosthesis	Reason for use of drug	Drug used	Route	Risk factor (%)
Alzoman (2011)	Cross- sectional	Riyadh/ Saudi Arabia	NR	88 (75)	58	Tooth extraction Endodontics Surgery Implant Restoration	Bone diseases/ Cancers	Alendronate Pamidronate	Oral/IV	Hypertension (47.7) Diabetes mellitus (36.4) Rheumatological diseases (34) Blood diseases (9.1) Cancer (9) Smoking (4.5)
Grant et al. (2008)	Cross- sectional	Nova York/ USA	1998-2006	115 (100)	67.4	Implant	NR	Alendronate Ibandronate Risedronate	Oral	Diabetes mellitus (0.9)
Ferlito et al. (2011)	Case series	Sicilia/ Italy	2007-08	43 (NR)	56.4 ± 5.8	Tooth extraction	Cancers	Zoledronate	IV	NR
Fugazzotto et al. (2007)	Case series	Milton and Hackensack/ USA	2005	61 (100)	67	Implant	NR	Alendronate Risedronate	Oral	NR
Hasegawa et al. (2013)	Cohort	Nagasaki/ Kobe Japan	NR	201 (91%)	16.2 ± 3.2	Tooth extraction	Osteoporosis	Alendronate Risedronate	Oral	NR
Hutcheson et al. (2014)	Cohort	Adelaide/ Australia	2007-2013	1900 (59.5)	68.5	Tooth extraction	Osteoporosis	Alendronate Risedronate	Oral	NR
Kang et al. (2020)	Cohort	Goyang/ Korea	2008-2017	420 (90.3)	69.05	Tooth extraction	Osteoporosis/ Cancers	Alendronate Ibandronate	Oral/IV	NR Steroids (9.1) Diabetes mellitus (18.2) Smoking (3.6)
Koka; Babu; Norell (2010)	Cohort	Rochester/ USA	2009	54 (100)	71	Implant	Osteoporosis	Alendronate	Oral	NR Steroids (9.1) Diabetes mellitus (18.2) Smoking (3.6)
Lazarovici et al. (2010)	Case series	Tel Hashomer/ Israel	2007-08	63 (80.8%)	63.4	Tooth extraction	Osteoporosis/ Cancers	Alendronate Risedronate Clodronate Pamidronate Zoledronate	Oral/IV	Steroids Chemotherapy
Lodi et al. (2010)	Case series	Milão/Italy	2006-09	15 (65.2)	68.2	Tooth extraction	Cancers	Zoledronate Pamidronate Clodronate	IV	NR

Migliorati et al. (2013)	Cohort	Fort Lauderdale (USA) Sudbury (Canada) Oslo (Noruega)	2007-11	53 (81.1)	40-92	Tooth extraction	Cancers/ Osteoporosis	NR	Oral/IV	NR
Mozzati, Arata, Gallesio (2012)	RCT	Torino/Italy	2005-09	176 (57.3)	44-83	Tooth extraction	Cancers	Zoledronate	IV	Smoking (0.6) Steroids (34) Chemotherapy (20.6)
Mozzati, Arata, Gallesio (2013)	RCT	Torino/Italy	2005-11	700 (96.7)	52-79	Tooth extraction	Osteoporosis	Alendronate Risedronate	Oral	Smoking (34.6) Steroids (15)
O'Connell et al. 2013	Case series	Dublin/Ireland	NR	22 (95.6)	59	Tooth extraction	Osteoporosis, Osteopenia	Alendronate Risedronate Zoledronate	Oral/IV	Steroids (NR)
Otto et al. (2015)	Case series	Munich/Germany	2007-13	72 (73.6)	67.5	Tooth extraction	Cancers/ Osteoporosis	NR	Oral/IV	Smoking (45) Steroids (55) Chemotherapy (45)
Saia et al. (2010)	Case series	Verona and Padua /Italy	2006-08	60 (70)	65.0	Tooth extraction	Cancers/ Osteomyelitis	*Risedronate **Zoledronate **Pamidronate **Neridronate	*Oral/**IV	Osteomyelitis (6.6)
Sanchis et al. (2014)	Case series	Valencia/Spain	2009-11	36 (61.2)	63.8	Tooth extraction	Cancers/ Crohn Disease	Zoledronate	IV	NR
Scoletta et al. (2011)	Case series	Turin/Italy	2007-09	45 (69.2)	64.8 ± 10.9	Tooth extraction	Cancers/ Paget's disease	Zoledronate Pamidronate	IV	Steroids (NR)
Scoletta et al. (2013)	Case series	Turin/Italy	2010-11	63 (71.4)	65.8 ± 8.8	Tooth extraction	Osteoporosis, Cancers	Zoledronate Pamidronate Ibandronate	IV	Steroids (NR)
Sedghizadeh et al. (2009)	Cohort	British Columbia/Canada	2008	208 (NR)	73.0	Tooth extraction and prosthesis	Osteoporosis	Alendronate	Oral	Diabetes mellitus (0.9) Steroids (0.5) Chemotherapy (0.9)
Shabestari et al. (2009)	Case series	Tehran/Iran	1998–2006	21 (100)	53	Implant	Osteoporosis	Alendronate	Oral	NR
Shudo et al. (2018)	Cohort	Hyogo/Japan	2014-17	132 (84.8)	71.9	Tooth extraction	Osteoporosis	Alendronate Ibandronate Risedronate Minodronate	Oral	Steroids (41) Diabetes mellitus (21) Rheumatoid (17) Lupus (3) Dialysis (2.2)

Siebert et al. (2015)	Cohort	Martin/ Slovakia	NR	12 (100)	≥ 54	Tooth extraction Implant	Osteoporosis	Zolendronate	IV	No
Vahtsevanos et al. (2009)	Cohort	Tessalônica/ Greece	2000-08	742 (NR)	NR	Tooth extraction Prosthesis	Cancers	Pamidronate Zoledronate Ibandronate	IV	Smoking (5.6)
Vescovi et al. (2013)	Case series	Parma/ Italy	2006-10	179 (82.5)	68.7 ± 11.3	Tooth extraction	Cancers, Paget's disease	Zoledronate Pamidronate Alendronate Risedronate Clodronate	Oral/IV	Hormonal therapy (NR) Chemotherapy (NR) Opioids (NR) Anticoagulants (NR) Smoking (16) Steroids (44) Chemotherapy (20) Diabetes mellitus (7) Alcohol (23)
Yamazaki et al. (2012)	Cohort	Kyoto/ Japan	2006-09	126 (81.7)	66	Tooth extraction	Cancers/ Osteoporosis	*Etidronate *Alendronate *Risedronate **Incadronate **Pamidronate **Zoledronate	Oral/IV	
Zahid; Wang; Cohen (2011)	Case series	Buffalo/ USA	1997-2008	25 (89)	56 ± 31	Implant	Osteoporosis	Alendronate	Oral	Smoking (8.5)

Sd: standard deviation. N: number of patients. Min: minimum. Máx: maximum. IV: Intravenous. NR: not reported. RCT: Randomized clinical trial.

Table 2. Risk of osteonecrosis of the jaw in patients using bisphosphonate undergoing dental surgery or due to trauma by dental prosthesis (n=27 studies)

Reference	Bisphosphonate (dosage or posology)	Treatment Duration (months)	Dental procedure (numbers of teeth)	Osteonecrosis (numbers)	Population/ total (%)	Follow-up (months)
Intravenous						
Ferlito et al. (2011)	Zoledronate (4mg)	16.2 ± 3.2	Tooth extraction (102)	None	0/43 (0)	12
Lazarovici et al. (2010)	Pamidronate (NR) Zoledronate (NR) Clodronate (NR) Zoledronate (NR)	48	Tooth extraction (NR)	Maxillary (NR) mandibular (NR)	14/27 (52)	±10
Lodi et al. (2010)	Pamidronate (NR) Clodronate (NR)	17.5	Tooth extraction (38)	None	0/23 (0)	7.6
Mozzati, Arata, Gallesio (2012)	Zoledronate (4mg each 3 weeks)	12	Tooth extraction (542)	Maxillary (0) mandibular (5)	5/176 (2.8)	60
O'Connell et al. (2013)	Zoledronate (4mg)	30	Tooth extraction (NR)	none	0/23 (0)	5
Sanchis et al. (2014)	Zoledronate (4mg/NR)	19.1 (avarage)	Tooth extraction (62)	Maxillary (3) mandibular (5)	8/34 (23.5)	48
Scoletta et al. (2011)	Zoledronate (4mg) Pamidronate (90mg)	19.6 ± 18.9	Tooth extraction (25)	mandibular (5)	5/65 (7.7)	13.1 ± 1.3
Scoletta et al. (2013)	Zoledronate (4mg) Pamidronate (90mg) Ibandronate (6mg)	16.8 ± 13.9	Tooth extraction (202)	mandibular (1)	1/63 (1.59)	12
Vahtsevanos et al. (2009)	Pamidronate (90mg/NR) Zoledronate (4mg/NR) Ibandronate (6mg/NR)	5	Tooth extraction (NR) Endodontics (NR)	Maxillary (NR) mandibular (NR)	46/114 (4.3) 19/405 (4.7)	NR
Oral/Intravenous						
Alzoman (2011)	Alendronate (4mg), Pamidronate (90mg)	30 (avarage)	Tooth extraction (NR) Endodontics (NR) Implantology (NR)	None	0/88 (0)	NR
Kang et al. (2020)	Alendronate (4mg) Ibandronate (6mg)	36	Tooth extraction (1.323)	Mandibular (1)	1/465 (0.2)	NR
Migliorati et al. (2013)	NR	30	Tooth extraction (NR)	Maxillary (NR) mandibular (1) Maxillary (NR) mandibular (NR)	1/92 (1.1)	NR
Otto et al. (2015)	NR	36.2 (avarage)	Tooth extraction (216)	Maxillary (NR) mandibular (NR)	3/72 (4.7)	14.5 (avarage)
Saia et al. (2010)	**Zoledronate. (58mg/NR) **Pamidronate (1.6g/NR) **Neridronate (1,075mg/NR) *Risedronate (5.0-8.7g/NR)	(NR)	Tooth extraction (185)	Maxillary (3) mandibular (6)	5/60 (8.3)	12

Vahsevanos et al. (2009)	Pamidronate (90mg/NR) Zoledronate (4mg/NR) Ibandronate (6mg/NR) Alendronate (NR) Clodronate (NR)	5	Trauma (NR)	Maxillary (NR) mandibular (NR)	24/223 (10.7)	NR
Vescovi et al. (2013)	Pamidronate (NR) Risedronate (NR) Zoledronate (NR)	1 to 92	Tooth extraction (589)	Maxillary (3) mandibular (2)	5/217 (2.3)	4–31
Yamazaki et al. (2012)	*Etidronate (200mg/day) *Alendronate (5mg/day) *Risodronate (2.5mg/day) **Incadronate (10mg/day) **Pamidronate (90mg/day) **Zoledronate (4mg/day)	4 to 45	Tooth extraction (NR)	Maxillary (NR) /mandibular (NR)	5/126 (3.9)	NR
Oral						
Grant et al. (2008)	Alendronate (NR) Ibandronate (NR) Risedronate (NR)	38	Implant (468)	None	0/115 (0)	> 48
Fugazzotto et al. (2007)	Alendronate (35 mg/ week) Risedronate (70mg/ week)	39	Implant (169)	None	0/61(0)	12-24
Hasegawa et al., (2013)	Alendronate (NR) Risedronate (NR) Minodronate (NR)	28.3 ± 29.2	Tooth extraction (434)	NR (1)	1/201 (0.5)	30
Hutcheson et al., (2014)	Alendronate (NR) Risedronate (NR)	± 60	Tooth extraction (2,461)	NR (4)	4/950 (0.4)	NR
Koka; Babu; Norell (2010)	Alendronate (70mg/ week)	36-60	Implant (121)	None	0/55	NR
Lazarovici et al. (2010)	Alendronate (NR) RisedronateNR) Clodronate (NR)	48	Tooth extraction (NR)	Maxillary (NR) mandibular (NR)	4/51 (7.8)	10
Mozzati, Arata, Gallesio (2013)	Alendronate (NR) Risedronate (NR)	24	Tooth extraction (1,480)	None	0/700 (0)	12–72
O'Connell et al. (2013)	Alendronate (NR) Risedronate (NR)	30	Tooth extraction (NR)	Maxillary (NR) mandibular (NR)	0/19 (0)	5
Sedghizadeh et al., (2009)	Alendronate (70mg/week)	12	Tooth extraction (66) Trauma (142)	Maxillary (2) mandibular (7)	4/66 (6.1) 5/142 (3.5)	NR
Shabestari et al. (2009)	Alendronate (35-70mg/ week)	20.5	Implant	None	0/21 (0)	NR

Siebert et al. (2015)	Zolendronate (5mg/year)	24-36	Implant (60) Tooth extraction (NR)	None	0/12 (0)	12
Shudo et al. (2018)	Alendronate (NR) Risedronate (NR) Minodronate (NR) Ibandronate (NR)	24 to 120	Tooth extraction (274)	None	0/132 (0)	3
Zahid; Wang; Cohen (2011)	Alendronate (70mg/week)	>48	Implant (51)	None	0/26 (0)	26

n: numbers of patients. Min: minimum. NR: not reported.

Risk of bias

Of the 8 items evaluated, most studies exhibited methodological bias for 5 them. The risk of bias mainly involved problems related to adequate sampling, appropriate sampling source, absence of the calculation of the sample size, unbiased measure of outcome and absence of description of estimated results together with confidence intervals, as well as description of subgroups. Most studies were of low methodological quality (n= 21) (Table 3).

Table 3. Risk of bias of studies (n= 27 studies)

References	Adequate sampling	Appropriate sampling source	Adequate sample size	Measure adequate of outcome	Unbiased measured of outcome	Adequate response rate	Description of confidence intervals and subgroups	Description of subjects and setting	Pontuation
Alzoman (2011)	No	No	No	No	No	NA	No	Yes	1 of 7
Grant et al. (2008)	No	No	No	No	No	No	No	Yes	1 of 8
Ferlito et al. (2011)	No	No	No	No	No	NA	No	Yes	1 of 7
Fugazzotto et al. (2007)	Yes	Yes	No	No	No	Yes	No	No	3 of 8
Hasegawa et al. (2013)	No	No	No	Yes	Yes	NA	No	Yes	3 of 7
Hutcheson et al. (2014)	Yes	Yes	NA	No	Yes	NA	No	Yes	4 of 6
Kang et al. (2020)	No	No	No	No	No	Yes	No	Yes	2 of 8
Koka et al. (2010)	Yes	Yes	Yes	No	No	Yes	No	Yes	5 of 8
Lazarovici et al. (2010)	No	No	No	Yes	No	NA	No	Yes	2 of 7
Lodi et al. (2010)	No	No	No	No	No	NA	No	No	1 of 7
Migliorati et al. (2013)	No	No	No	No	Yes	NA	Yes	Yes	3 of 7
Mozzati; Arata; Gallesio (2012)	NA	NA	No	Yes	No	Yes	No	Yes	3 of 6
Mozzati; Arata; Gallesio (2013)	NA	NA	No	Yes	No	Yes	No	Yes	3 of 6
O'Connell et al. (2013)	Yes	No	No	Yes	No	Yes	No	Yes	4 of 8
Otto et al. (2015)	No	No	No	Yes	No	NA	No	Yes	2 of 7
Sedghizadeh et al. (2009)	No	No	No	Yes	No	NA	No	No	2 of 7
Saia et al. (2010)	No	No	No	Yes	No	NA	Yes	Yes	3 of 7
Sanchis et al. (2014)	No	No	No	Yes	No	NA	Yes	Yes	3 of 7
Scoletta et al. (2011)	Yes	No	No	Yes	Yes	Yes	No	No	3 of 8
Scoletta et al. (2013)	Yes	No	No	No	No	Yes	No	Yes	3 of 8
Shabestari et al. (2010)	No	No	No	No	No	Yes	Yes	No	2 of 8
Shudo et al. (2018)	No	No	No	Yes	Yes	NA	No	Yes	3 of 7
Siebert et al. (2013)	No	No	No	Yes	No	Yes	No	Yes	3 of 8
Vahtsevanos et al. (2009)	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	7 of 8
Vescovi et al. (2013)	Yes	Yes	No	No	No	Yes	No	No	3 of 8
Yamazaki et al. (2012)	No	No	No	Yes	Yes	NA	Yes	Yes	4 of 7
Zahid et al. (2011)	Yes	Yes	Yes	No	No	No	Yes	Yes	5 of 8

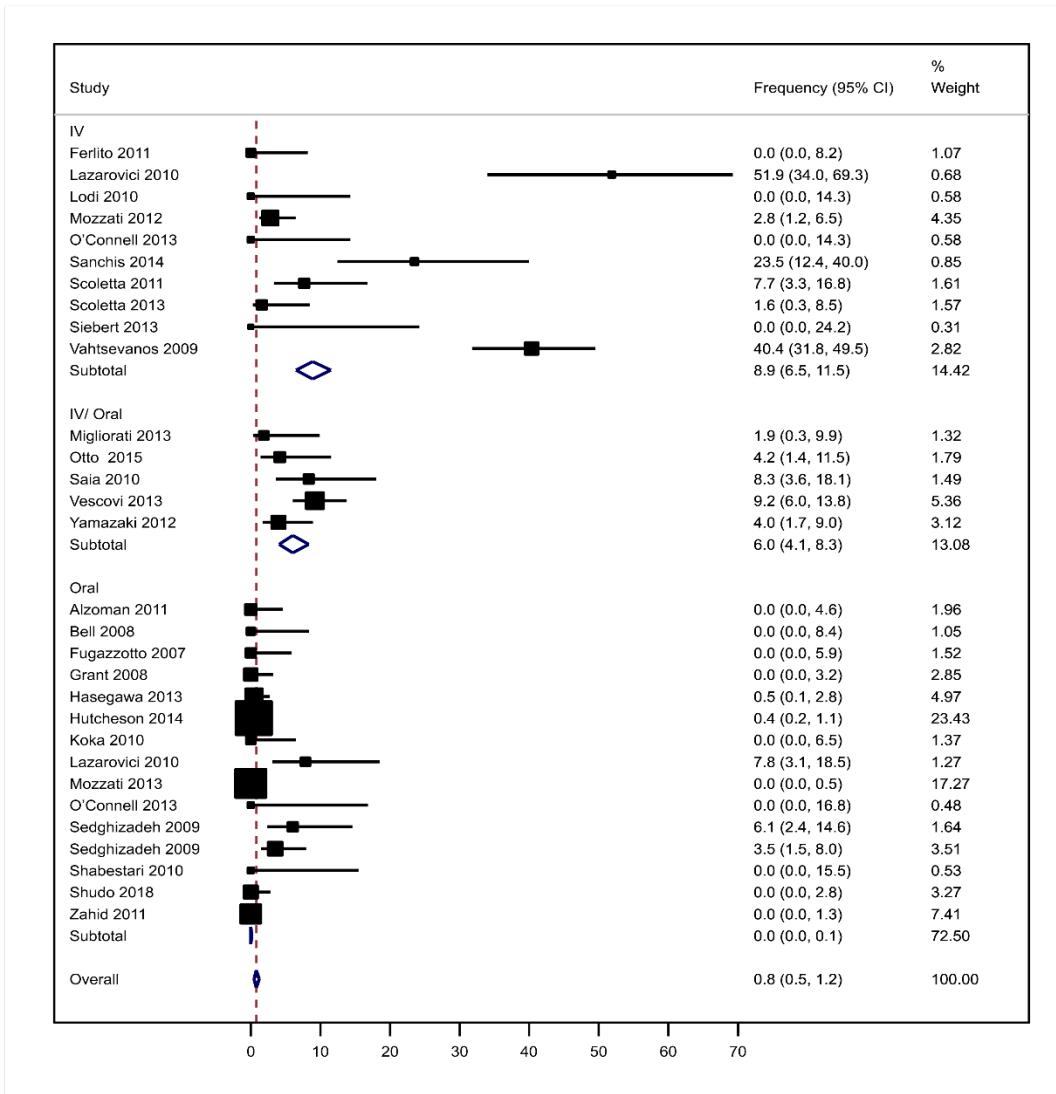
NA: not applicable

Risk of oral osteonecrosis

The risk of oral osteonecrosis in bisphosphonate users who underwent dental procedures was 0.8% (95% CI: 0.5 to 1.2%), proving higher for intravenous bisphosphonate [8.9% (95% CI: 6.5 to 11.5%)] compared to oral bisphosphonate [0.0% (95% CI: 0.0 to 0.1%)] (Figure 2).

The heterogeneity between the studies was 94.9% for those that reported the intravenous route, 54.2% in those that used the intravenous and oral routes and 64.7% for those that reported the oral route only.

Figure 2. Meta-analysis of the prevalence of the jaw osteonecrosis in bisphosphonate users undergoing dental procedures (n= 27 studies)



The risk of oral osteonecrosis in bisphosphonate users who underwent the tooth extraction procedure was (1.1%). Among the main bisphosphonates prescribed, there was a higher risk of osteonecrosis associated with the use of zoledronate compared to alendronate, which is explained by their different routes of administration. Regarding treatments with bisphosphonates, the risk of osteonecrosis was higher in cancer patients (Table 4).

Table 4. Meta-analysis of the prevalence of the jaw osteonecrosis in bisphosphonate users undergoing dental procedures, in selected subgroups (n= 27 studies)

Subgroups (number of studies)	% Frequency (95% IC)	Heterogeneity (%)
Dental procedures		
Extraction (n=21)	1.1 (0.7 to 1.6)	91.1
IV	8.9 (6.5 to 11.5)	
IV/Oral	6.0 (4.1 to 8.3)	
Oral	0.0 (0.0 to 0.2)	
Implant (n= 7)	0.0 (0.0 to 0.0)	0
IV	0.0 (0.0 to 24.2)	
Oral	0.0 (0.0 to 0.1)	
Bisphosphonates more used		
Alendronate (n=17)	0.2 (0.0 to 0.5)	82.6
Oral	0.0 (0.0 to 0.1)	
IV/Oral	7.2 (4.8 to 10.0)	
Zoledronate (n=13)	8.0 (6.2 to 9.9)	92.2
IV	8.9 (6.5 to 11.5)	
IV/Oral	7.2 (4.8 to 10.0)	
Treatments		
Osteoporosis (n=16)	0.2 (0.0 to 0.5)	78.4
IV/Oral	5.8 (3.8 to 8.2)	
IV	0.0 (0.0 to 24.2)	
Oral	0.0 (0.0 to 0.2)	
Cancers (n=14)	7.6 (5.9 to 9.4)	90.2
IV	9.6 (7.0 to 12.5)	
IV/Oral	6.0 (4.1 to 8.3)	

95% IC: 95% confidence interval. IV: intravenous

The meta-regression showed no change in the risk of oral osteonecrosis in relation to duration of treatment with bisphosphonates (ranging from 5 to 60 months) ($p= 0.540$) (Figure 3).

Figure 4 shows that there was no suspected publication bias (Egger test, $p= 0.107$).

Figure 3. Risk of the jaw osteonecrosis in patients undergoing dental procedures in relation to the duration of treatment with bisphosphonates (n= 27 studies)

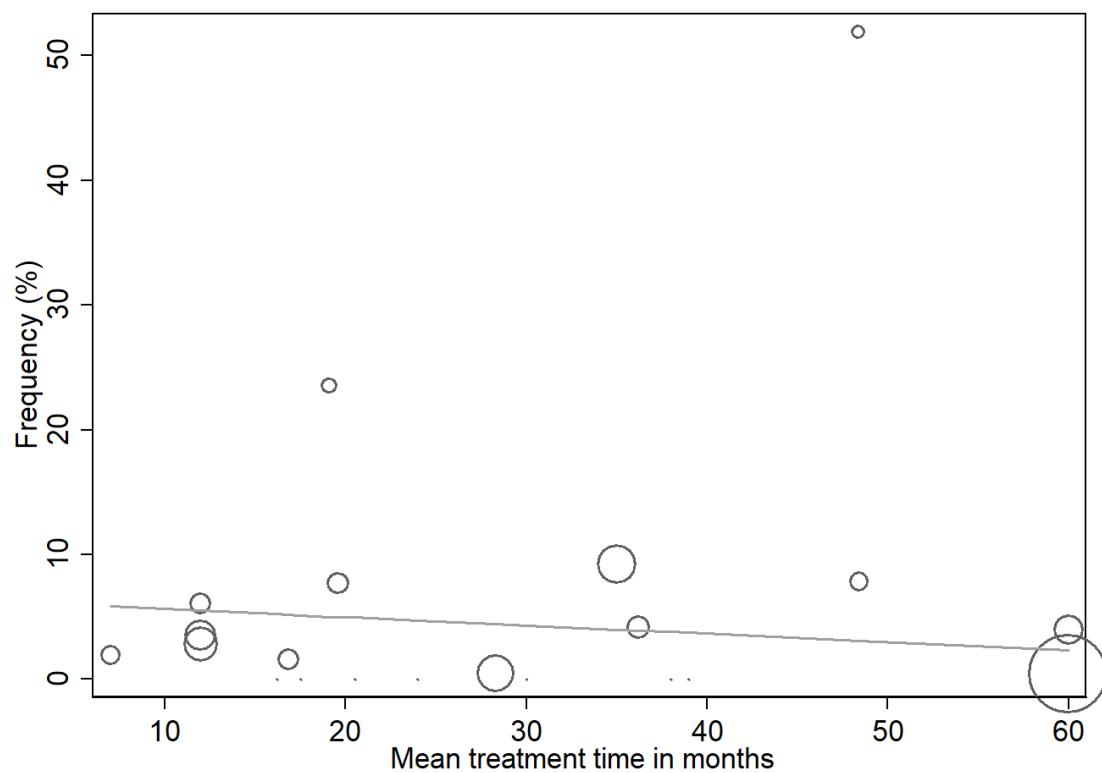
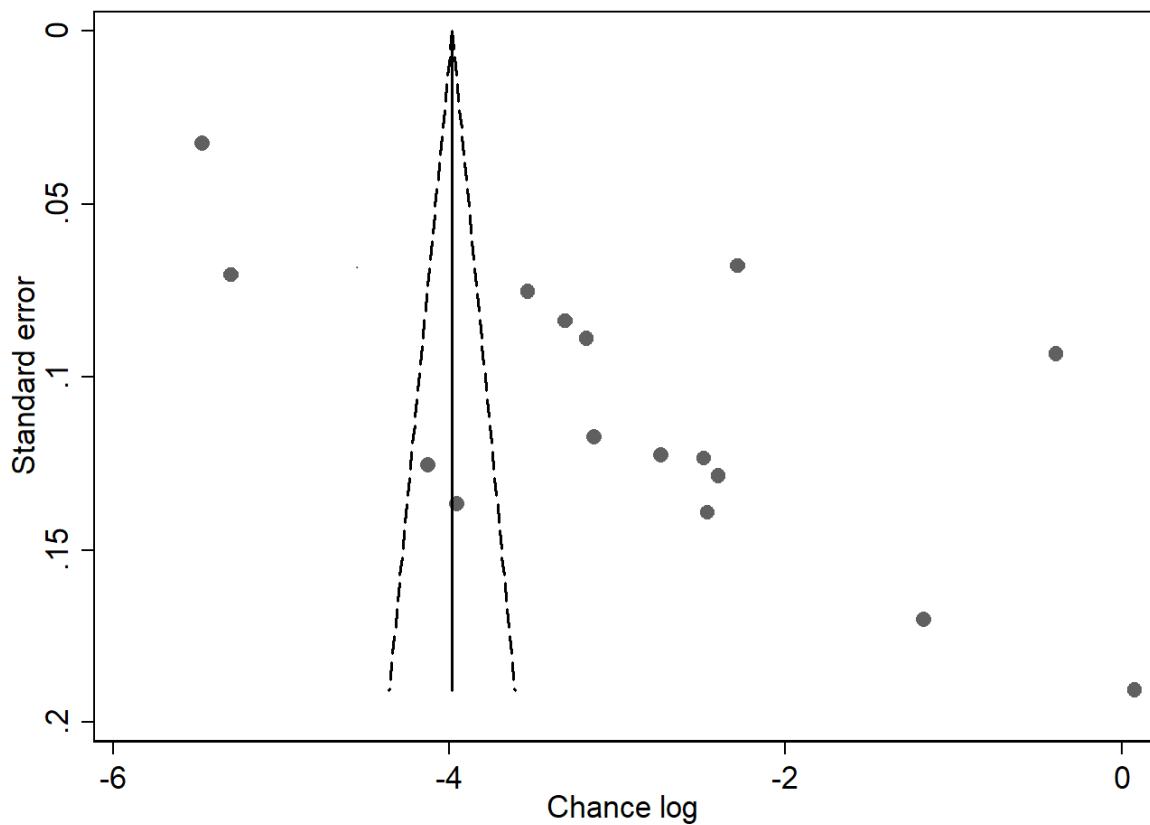


Figure 4. The publication bias was assessed by visual inspection of funnel plots (n= 27 studies)



DISCUSSION

Main findings and comparison against the literature

In a population of 4,865 participants, the risk of osteonecrosis of the jaw in bisphosphonate users who underwent dental procedures was 0.8%, proving higher risk with the use intravenous bisphosphonates (8.9%) compared to oral use (0.0%). These findings are based on studies that were high heterogeneity and in generally, of low methodological quality. The main methodological problems found involved sample selection and absence of detailed description of results.

Dental extraction was the most commonly reported by the primary studies (91.1%) with frequency of oral osteonecrosis in 1.1% of patients undergoing this procedure. There was a higher risk of osteonecrosis with the use of zoledronate compared to alendronate, explained by their different routes of administration. Too the risk of osteonecrosis was higher in the population undergoing treatment for cancers compared to osteoporosis, explained by the fact that drugs for treating cancer are administered predominantly by the intravenous route.

A similar systematic review reported a higher risk of osteonecrosis of the jaw after dental extraction in patients treated with anti-resorptive agents for cancer (3.2%) than for osteoporosis (0.15%). The study included only patients undergoing tooth extraction and investigated other anti-resorptive agents (Gaudin et al., 2015). By contrast, the present study determined osteonecrosis risk in bisphosphonate users submitted to any dental intervention. We found greater osteonecrosis risk in both cancer patients (7.6%) and those treated for osteoporosis (0.2%) compared with the previous review.

According to the literature periodontal disease, surgical procedure and poorly fitting removable prosthesis can be considered risk factors for oral osteonecrosis in patients undergoing treatment with bisphosphonates (AMERICAN DENTAL ASSOCIATION COUNCIL ON SCIENTIFIC AFFAIRS, 2019; SAIA et al., 2010). Dentoalveolar surgery is considered an invasive intervention which can traumatize hard and soft tissues and thus pose a risk for developing maxillary osteonecrosis in anti-resorptive users, since the use of these drugs can hinder tissue repair (VAHTSEVANOS et al., 2009; SAAD et al., 2012; FEHM et al., 2009).

Systematic review encompassing 4,106 participants with oral osteonecrosis identified 39 possible risk factors for osteonecrosis, 11 of which were related to dental procedures. Of these, dental extraction followed by periodontal disease predominated, highlighting that oral health care, reducing inflammation and treating infection can avoid the need for more complex treatment, thereby eliminating or minimizing these risks (MCGOWAN; MCGOWAN; IVANOVSKI, 2018).

The literature has shown that patients submitted to dental procedures prior to the use of anti-resorptive medications and/or antiangiogenic agents had lower rate of oral osteonecrosis (0.9%) than a group undergoing dental intervention after receiving medication therapy (10.5%) (OWOSHO et al., 2018). Although this finding is based on the report of a single study in a sample of 273 patients, it serves to highlight the importance of investigating which prophylactic measures are effective for reducing the risk of oral osteonecrosis.

In the present study, no association between the increased of risk of adverse effects and longer treatment time with the drugs was found. According to Sedghizadeh et al. (2009) and Vahtsevanos et al. (2009), short-term use of bisphosphonates can lead to osteonecrosis in patients undergoing dental extractions or suffering trauma due to dentures. In addition, another study reported that, although there were no cases of

oral osteonecrosis in patients submitted to dental procedures receiving bisphosphonates orally, healing of the surgical site after dental extraction was slower (SHUDO *et al.*, 2018).

The present study originally sought to confirm a causal relationship between dental procedures as risk factor for oral osteonecrosis in bisphosphonate users, compared to bisphosphonate users not undergoing these procedures. However, the absence of this information in most of the primary studies precluded confirmation of this relationship. Six cohort studies had control groups in which patients had been submitted only to dental procedure (HASEGAWA *et al.*, 2013; KOKA *et al.*, 2010; MIGLIORATI *et al.*, 2013; SEDGHIZADEH *et al.*, 2009; SIEBERT *et al.*, 2013; Yamazaki *et al.*, 2012). In these studies, patients of intervention group had undergone dental extraction or implant, but reported the use of different bisphosphonates and doses administered. In this way, the meta-analysis could not be performed.

Strengths and limitations of this study

The method employed in the present review comprised explicit eligibility criteria; comprehensive search on databases and assessment in pairs and independently, of the selected studies; increasing of the confidence that studies satisfying the eligibility criteria were included in the review. Also, a detailed analysis of risk of bias of the primary studies was carried out.

The main limitations of the study were the absence of a detailed description of the information from primary studies, along with issues related to their methodological rigor. Consequently, it was not possible to estimate the risk of oral osteonecrosis according to the bisphosphonates used, since most studies described use of more than one bisphosphonate and did not report the cases of osteonecrosis by drug used. In general, the studies did not report the dose or posology prescribed, while the duration of use of each drug was not available for some studies. Similarly, cohort studies differed in bisphosphonates used, making not possible to confirm the dental procedures as risk factor for developing osteonecrosis.

Implications for clinical practice and research

Knowledge on the prevalence of this adverse effect is important for prescribers, dental surgeons and other health professionals to guide the devising of preventive strategies. Patients and prescribers can be unaware of the potential oral repercussions this class of drug can have, significantly impacting the quality of life of those affected (MALLYA; TETRADIS, 2018).

Health professionals should emphasize to patients the importance of preventive treatment centered on good oral hygiene, thereby avoiding the need for dental procedures, and also orient them on oral trauma prevention. Moreover, patients and dentists should work together toward maintaining good oral health (SEDGHIZADEH *et al.*, 2009; MALLYA; TETRADIS, 2018).

A host of prophylactic measures can be implemented alone or in association, such as upon conclusion of dental treatment (restorative therapy, root canal treatment, periodontitis therapy or dental extraction, etc.), prior to anti-resorptive or antiangiogenic therapy or shortly after commencing treatment. For more invasive dental extraction, suspensions of anti-resorptive or antiangiogenic agents are recommended before dentoalveolar surgical procedures (BETH-TASDOGAN *et al.*, 2017).

In cases when the disease is already established, it is recommended to control infection, minimize progression of the necrosis and promote tissue healing. Standard treatment consists of intervention using systemic antibiotics, oral antiseptics, associated with a procedure such as surgical debridement or osseous resection of the lesion (RUGGIERO *et al.*, 2014). In order to reduce wound exposure to bacteria, reconstructive surgery techniques can be used to provide lesion closure and promote better healing (BETH-TASDOGAN *et al.*, 2017).

This review highlights the need for further primary studies to confirm the role of dental procedures in increasing the risk of oral osteonecrosis, given that the reports found involved small samples and lacked details on the bisphosphonates used, their doses and duration of use. In addition, there are few longitudinal studies comparing the exposure group versus not exposure to dental procedure, precluding meaningful conclusions on the causal relationship between dental procedures and osteonecrosis.

Within the limitations of the study, the present study serves to aid prescribers, dental surgeons, other health professionals and patients in providing information on the risks of bisphosphonate use in patients undergoing dental interventions, besides identifying areas requiring future study.

CONCLUSIONS

A higher risk of oral osteonecrosis was associated with the use of intravenous bisphosphonates in patients undergoing dental extraction, the most commonly dental intervention reported procedure in the studies. However, primary studies providing description more detailed of the bisphosphonates used, involving larger samples and

having greater methodological rigor are needed to determine whether there is a higher risk of oral osteonecrosis in bisphosphonate users submitted to dental procedures.

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Conflit of interest

The authors declare no conflict of interest.

6 CONSIDERAÇÕES FINAIS

O presente estudo determinou maior risco de osteonecrose de maxilares com o uso de bisfosfonatos intravenosos comparado ao uso oral, principalmente em pacientes submetidos a extração dental, procedimento mais relatado pelos estudos.

Observou-se maior risco de osteonecrose oral com o uso do zoledronato em relação ao alendronato que pode ser justificado pelo uso de diferentes vias de administração.

O risco de osteonecrose foi maior na população em tratamento para cânceres em comparação com a população em tratamento da osteoporose. Isto pode ser justificado pelo fato de que os medicamentos usados para tratamento de cânceres são principalmente utilizados pela via intravenosa.

Os achados desta revisão se basearam em estudos que em geral, apresentaram baixa qualidade metodológica e alta heterogeneidade. Os principais problemas metodológicos observados foram relacionados à seleção da amostra e ausência de descrição detalhada dos resultados.

Não foi possível estabelecer relação causal do procedimento odontológico como fator de risco para a osteonecrose oral em usuários de bisfosfonatos comparado a uma população que faz uso de bisfosfonatos, mas não foi submetida a estes procedimentos.

Em procedimentos odontológicos mais invasivos recomenda-se a suspensão destes medicamentos, antes da sua realização. Com a osteonecrose oral instalada, recomenda-se controlar a infecção, minimizar a progressão da necrose e promover a cicatrização do tecido.

Conhecer a frequência da ocorrência deste efeito adverso é relevante para profissionais de saúde e pacientes, a fim de demonstrar a necessidade de medidas de prevenção da osteonecrose oral.

Desta forma, prescritores devem alertar os pacientes quanto a importância do tratamento odontológico preventivo antes do início da terapia com bisfosfonatos ou o mais rápido possível, após o seu início.

Os achados demonstraram a necessidade de estudos primários com descrição detalhada dos bisfosfonatos utilizados e das doses e com ajustes metodológicos, bem

como, de estudos longitudinais que permitam a comparação entre os grupos exposição e controle, identificando lacunas para que pesquisas futuras sejam realizadas.

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ANEXO 1. ORIENTAÇÕES PARA APRESENTAÇÃO DE TESES DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS FARMACÉUTICAS DA UNIVERSIDADE DE SOROCABA

As dissertações/teses do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (PPGCF-Uniso) poderão ser apresentadas em dois formatos: o tradicional ou em formato de artigo(s) científico(s).

Os trabalhos de investigação que possam resultar em patentes poderão ser apresentados na forma convencional, a critério do grupo de pesquisadores envolvidos, reservadas as particularidades exigidas em relação ao sigilo.

O formato tradicional segue o padrão descrito nas normas do “Manual para normalização de trabalhos acadêmicos” da Universidade de Sorocaba.

As dissertações entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de pelo menos um artigo em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e podem ser inseridos no idioma e na formatação estabelecida pelo(s) respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

As teses entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de pelo menos dois artigos em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e devem ser inseridos no idioma e na formatação estabelecida pelo(s) respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

Para aclarar membros da banca que desconhecem esta versão alternativa da dissertação/tese, recomenda-se anexar este documento no final das versões encaminhadas aos membros da banca.

A dissertação/tese no formato de artigo(s) científico(s) deverá possuir os elementos apresentados no Quadro 1.

Quadro 1: Elementos presentes na dissertação/tese segundo formato adotado pelo Programa de Pós-graduação em Ciências Farmacêuticas.

	<p>1. <i>Introdução ou apresentação</i>: trata-se da parte inicial do texto com formulação clara e simples do tema investigado, constando a delimitação do assunto tratado, sua relevância e justificativa.</p> <p>2. <i>Revisão de literatura</i>: quando a revisão de literatura for concebida como artigo de revisão, este item deverá ser incluído no item resultado(s).</p> <p>3. <i>Objetivos</i>: geral e específico</p> <p>4. <i>Material e Métodos (opcional)</i>. Quando parte dos resultados não for apresentada no formato de artigo, este item deverá ser incluído após os objetivos específicos. Quando o autor quiser apresentar o(s) método(s) de forma mais detalhada do que no artigo, este item pode também ser apresentado em separado.</p>
<i>Elementos textuais</i>	<p>5. <i>Resultados (pode ser apresentado no formato de artigos)</i>: deve(m) ser inserida(s) a(s) cópia(s) de artigo(s) derivado(s) da dissertação, previamente publicados, submetidos ou não para publicação em revistas científicas. Sugere-se que cada artigo seja antecedido de uma breve apresentação seguida dos elementos de identificação do artigo (autores, título, revista de publicação, volume, páginas). Os artigos anexados poderão ser apresentados nos formatos exigidos pelas revistas, as quais os artigos foram publicados e/ou submetidos. Parte dos resultados pode ser apresentada em separado dos artigos, quando conveniente.</p> <p>6. <i>Discussão (opcional)</i>: O autor pode ampliar a discussão dos resultados, quando conveniente.</p> <p>7. <i>Conclusão ou Considerações finais</i>: esta parte deverá conter a conclusão do trabalho ou as considerações do autor sobre os resultados alcançados frente aos objetivos propostos.</p>
<i>Elementos pós-textuais</i>	<p>8. <i>Referências</i>: Devem seguir as normas do “Manual para normalização de trabalhos acadêmicos” da Universidade de Sorocaba. Não devem ser inseridas as referências apresentadas nos artigos.</p> <p>9. <i>Apêndices (Opcional)</i></p> <p>10. <i>Anexos (Opcional)</i></p>

ANEXO 2: DECLARAÇÃO DE POTENCIAIS CONFLITOS DE INTERESSE

AUTORES: LÚCIO HENRIQUE IVES MARTINS E CRISTIANE DE CASSIA BERGAMASCHI MOTTA

1. Você já aceitou de uma instituição, que pode se beneficiar ou se prejudicar financeiramente, algum dos benefícios abaixo?

a) Reembolso por comparecimento a eventos na área de sua pesquisa

Não / Não

b) Honorários por apresentação, consultoria, palestra ou atividades de ensino

Não / Não

c) Financiamento para redação de artigos ou editorias

Não / Não

d) Suporte para realização ou desenvolvimento de pesquisa na área

Não / Não

e) Recursos ou apoio financeiro para membro da equipe

Não / Não

f) Algum outro benefício financeiro

Não / Não

2. Você possui apólices ou ações de alguma empresa que possa de alguma forma ser beneficiada ou prejudicada?

Não / Não

3. Você possui algum direito de propriedade intelectual (patentes, registros de marca, royalties)?

Não / Não

4. Você já atuou como perito judicial?

Não / Não

5. Você participa, direta ou indiretamente, de algum grupo citado abaixo cujos interesses possam ser afetados pela sua atividade?

a) Instituição privada com ou sem fins lucrativos

Não / Não

b) Organização governamental ou não-governamental

Não / Não

c) Produtor, distribuidor ou detentor de registro

Não / Não

d) Partido político

Não / Não

e) Comitê, sociedade ou grupo de trabalho

Não / Não

f) Outro grupo de interesse

Não / Não

6. Você poderia ter algum tipo de benefício clínico?

Não / Não

7. Você possui uma ligação ou rivalidade acadêmica com alguém cujos interesses possam ser afetados?

Não / Não

8. Você possui profunda convicção pessoal ou religiosa que pode comprometer o que você irá escrever e que deveria ser do conhecimento público?

Não / Não

9. Existe algum aspecto do seu histórico profissional, que não esteja relacionado acima, que possa afetar sua objetividade ou imparcialidade?

Não / Não

10. Sua família ou pessoas que mantenha relações próximas possui alguns dos conflitos listados acima?

Não / Não

Confirmamos que todas as informações declaradas são verdadeiras e completas. Comprometemo-nos a informar se houver qualquer mudança em algumas das questões desta declaração que possa influenciar o interesse durante o desenvolvimento das atividades do Programa de Pós-Graduação em Ciências Farmacêuticas – Nível Mestrado da Universidade de Sorocaba.

Sorocaba, 02 de fevereiro de 2021.

Profa. Dra. Cristiane de Cássia Bergamaschi Motta

Orientadora - Universidade de Sorocaba (UNISO)

Lúcio Henrique Ives Martins

Estudante de Pós-Graduação em Ciências Farmacêuticas - curso de Mestrado
Universidade de Sorocaba (UNISO)

ANEXO 3: REGISTRO NO PROSPERO



1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.
Risk of osteonecrosis in bisphosphonate users submitted to dental procedure:
systematic review

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.
Risco de osteonecrose em pacientes usuários de bifosfonato submetidos a
procedimento cirúrgico odontológico.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

4. * Anticipated complete date.

Give the date by which the review is expected to be completed.

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No

Data analysis	No	No
---------------	----	----

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Cristiane de Cossia Bergamaschi

7. Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:
cristiane.motta@prof.uniso.br

8. Named contact address

Give the full postal address for the named contact.

São Paulo, avenue, 4461 Além Ponte, Sorocaba, SP, Brazil

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.
 55 19 981458482

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available.
 This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Sorocaba

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

NOTE: email and country are now mandatory fields for each person.

Professor Cristiane de Cássia Bergamaschi.

University of Sorocaba Lucio Henrique Ives Martins.

University of Sorocaba

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

University of Sorocaba.

Grant number(s) 13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

Delaine Cristina Ferreira and Reginaldo Franquez. University of Sorocaba

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

What is the risk of osteonecrosis after dental surgery in users of bisphosphonates?

16. * Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment).

Searches will be performed on MEDLINE (via Ovid), EMBASE (via Ovid), Web of Science, Scopus, Virtual Health Library and bank of thesis of coordination for the improvement of higher level personnel (Capes). The search will be no restriction of language or date of publication. Other search resources that will be used: OpenGrey and the Gray Literature Report. In addition, reviewers

will review the list of references or citations found in secondary studies to verify and identify potentially eligible studies. When necessary, the main authors of the studies will be contacted for further information.

17. URL to search strategy.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Oral osteonecrosis induced by bisphosphonates was first reported in 2003, when 36 mandibular and maxillary bone lesions were demonstrated in patients using pamidronate or zoledronate, characterizing the lesions as resulting from a serious and unknown adverse effect. It is considered a complication associated with bisphosphonate therapy and has a significant and debilitating impact on patients.

19. *Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Adult patients, of both sex, undergoing dental procedures and exposed to bisphosphonate therapy, regardless of the route of administration. Patients undergoing drugs other than bisphosphonates will be excluded from this study.

20. *Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Any dental surgical intervention.

21.* Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

No dental intervention or other surgical intervention.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study

types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Observational studies (case-control, cohort and cross-sectional studies) and randomized controlled clinical trials will be included.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The risk of osteonecrosis of the mandible or maxilla in patients submitted dental procedures in relation to bisphosphonate therapy and route of administration.

Measures of effect

Please specify the effect measure(s) for your main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat'.

Hazard ratio.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review.

None

*** Measures of effect**

Please specify the effect measure(s) for your additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat'.

Not applicable.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Reviewers will evaluate, in pairs and independently, the potentially relevant titles and abstracts and will apply the eligibility criteria. The full text of potentially eligible articles will be obtained. These reviewers, too in pairs and independently, will assess the eligibility of each full text and resolve disagreements by consensus. A

third reviewer can assist with the final decision, if necessary in case of duplicate publication, the article with the most complete data will be used. The same reviewers, in pairs and independently,

will extract data from the included studies, using a pretested data extraction form and with instructions. Disagreements will be resolved by consensus and any unresolved issues will be referred to a third reviewer. The main data extracted will be about: participants (age, sex, disease), studies (study design, year of publication, country and institution that it was performed), bisphosphonate used, dental procedure, measured outcomes and risk of bias.

27. * Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

To assess the quality of the studies, we will adapt the tool standardized by Loney et al. (1998). To determine the relative weighting of each item for the scoring system, two authors will recommend weights for each item. The risk of bias will also be done, independently and in duplicate, by at least two reviewers. The observed differences will be resolved by consensus between the reviewers.

28. * Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

The heterogeneity between the studies will be evaluated associated to the estimates of the effects grouped using a χ^2 test and the I^2 statistic (Higgins, Thompson, 2002) and will be classified as: 0 to 25% (low heterogeneity); 50% (moderate heterogeneity); and 75% (high heterogeneity) (Higgins et al., 2003). If substantial levels of heterogeneity are found in the investigated results, the reasons will be explored (subgroup analysis and investigation of heterogeneity). Publication bias will be assessed through visual inspection of funnel charts for the results covered in 10 or more studies. The meta-analysis will be carried out in Stata Program v.14.0. If the meta-analysis is not appropriate due to excessive heterogeneity, the information will be summarized in tables and through narrative synthesis.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach. The results will be analyzed separately according to the study design, bisphosphonate used and route of administration.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Brazil

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

No I do not make this file publicly available until the review is complete

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences. Provide statistical data on osteonecrosis after a dental surgical procedure so that dental surgeons have knowledge and look for ways to proceed when they need to intervene in bisphosphonate users.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Osteonecrosis, Bisphosphonates, Prevalence, Jaw, Systematic Review

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For new registrations the review must be Ongoing. Please provide anticipated publication date Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint. Give the link to the published review.

APPENDIX A. PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	23
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	24
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	25
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	25
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	26
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	26, 27
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	27
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	27
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	28

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	28
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	28
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	29
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	29
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	29
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	29
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	29
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	31
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	32
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	32
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	40
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	40-41
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	41

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	41
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	41
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	42
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	44
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	46

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.1000097.

APPENDIX B: DATABASE SEARCH STRATEGY

Quadro 6 - Search strategy used at MEDLINE

1	Osteonecroses.mp. or exp Osteonecrosis	(10074)
2	Bone Necrosis.mp. or exp Osteonecrosis	(10329)
3	Necrosis, Avascular, of Bone.mp. or exp Osteonecrosis	(10066)
4	Avascular Necrosis of Bone.mp. or exp Osteonecrosis	(10093)
5	Bone Avascular Necrosis.mp. or exp Osteonecrosis	(10067)
6	necrosis, Aseptic, of Bone.mp. or exp Osteonecrosis	(10066)
7	Aseptic Necrosis of Bone.mp. or exp Osteonecrosis	(10070)
8	Bone Aseptic Necrosis.mp. or exp Osteonecrosis	(10066)
9	Bone Necroses.mp. or exp Osteonecrosis	(10070)
10	Necroses, Bone.mp. or exp Osteonecrosis	(10067)
11	Kienbock Disease.mp. or exp Osteonecrosis	(10086)
12	Kienbock's Disease.mp. or exp Osteonecrosis	(10184)
13	Kienboeck Disease.mp. or exp Osteonecrosis	(10066)
14	Kienboeck's Disease.mp. or exp Osteonecrosis	(100680)
15	Kienboecks Disease.mp. or exp Osteonecrosis	(10068)
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	(10506)
17	Bisphosphonate Associated Osteonecrosis of the Jaw.mp. or exp "Bisphosphonate-Associated Osteonecrosis of the Jaw"	(1133)
18	Alendronate.mp. or exp Alendronate	(4550)
19	Bevacizumab.mp. or exp Bevacizumab	(13996)
20	Denosumab.mp. or exp Denosumab	(1985)
21	Ibandronate.mp. or exp Ibandronic Acid	(1000)
22	Neridronate.mp.	(84)
23	Pamidronate.mp. or exp Pamidronate	(2394)
24	Residronate.mp.	(7)
25	Sirolimus.mp. or exp Sirolimus	(19951)
26	Sorafenib.mp. or exp Sorafenib	(6340)
27	Sunitinib.mp. or exp Sunitinib	(4767)
28	Tiludronic acid.mp.	(83)
29	Zoledronic Acid.mp. or exp Zoledronic Acid	(3951)
30	Everolimus.mp. or exp Everolimus	(5717)
31	Lenalidomide.mp. or exp Lenalidomide	(3521)
32	Pazopanib.mp.	(1196)
33	Ramucirumab.mp.	(398)
34	Thalidomide.mp. or exp Thalidomide	(8550)
35	Olpadronate.mp.	(51)
36	Etidronate.mp. or exp Etidronic Acid	(2029)

37	Clodronate.mp. or exp Clodronic Acid	(1936)
38	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	(67507)
39	16 and 38	(1716)

Quadro 7 - Search strategy used at EMBASE

1	Osteonecroses.mp. or exp bone necrosis	(29000)
2	Bone Necrosis.mp. or exp bone necrosis	(29357)
3	Necrosis, Avascular, of Bone.mp.	(3)
4	Avascular Necrosis of Bone.mp.	(268)
5	Bone Avascular Necrosis.mp.	(14)
6	Necrosis, Aseptic, of Bone.mp.	(0)
7	Aseptic Necrosis of Bone.mp.	(76)
8	Bone Aseptic Necrosis.mp. or exp aseptic necrosis	(1824)
9	Bone Necroses.mp. or exp bone necrosis	(28981)
10	Necroses, Bone.mp.	(4)
11	Kienbock Disease.mp. or exp Kienboeck disease	(917)
12	Kienbock's Disease.mp.	(704)
13	kienboeck Disease.mp. or exp Kienboeck disease	(829)
14	Kienboeck's Disease.mp. or exp Kienboeck disease	(833)
15	Kienboecks Disease.mp. or exp Kienboeck disease	(833)
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	(30461)
17	Bisphosphonate Associated Osteonecrosis of the Jaw.mp. or exp jaw osteonecrosis	(4819)
18	Alendronate.mp. or exp alendronic acid	(16264)
19	Bevacizumab.mp. or exp bevacizumab	(55051)
20	Denosumab.mp. or exp denosumab	(8186)
21	Ibandronate.mp. or exp ibandronic acid	(5251)
22	Neridronate.mp. or exp neridronic acid	(442)
23	Pamidronate.mp. or exp pamidronic acid	(10513)
24	Residronate.mp.	(32)
25	Sirolimus.mp. or exp rapamycin	(52666)
26	Sorafenib.mp. or exp sorafenib	(27587)
27	Sunitinib.mp. or exp sunitinib	(21815)
28	Tiludronic acid.mp. or exp tiludronic acid	(859)
29	Zoledronic Acid.mp. or exp zoledronic acid	(15722)
30	exp everolimus/ or Everolimus.mp.	(27968)
31	Lenalidomide.mp. or exp lenalidomide	(17858)
32	exp pazopanib/ or Pazopanib.mp.	(7206)
33	Ramucirumab.mp. or exp ramucirumab	(2249)
34	exp thalidomide/ or Thalidomide.mp.	(27703)
35	Olpadronate.mp. or exp olpadronic acid	(271)
36	Etidronate.mp. or exp etidronic acid	(7018)
37	Clodronate.mp. or exp clodronic acid	(6704)

38	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37	(232095)
39	16 and 38	(6202)

Quadro 8 - Search strategy used at WEB OF SCIENCE

TÓPICO: (Bisphosphonate Associated Osteonecrosis of the Jaw OR Alendronate OR Zoledronic Acid OR Everolimus OR Lenalidomide OR Pazopanib OR Ramucirumab OR Thalidomide OR Olpadronate OR Etidronate OR Clodronate Bevacizumab OR Denosumab OR Ibandronate OR Neridronate OR Pamidronate OR Residronate OR Sirolimus OR Sorafenib OR Sunitinib OR Tiludronic acid OR Zoledronic Acid OR Everolimus OR Lenalidomide OR Pazopanib OR Ramucirumab OR Thalidomide OR Olpadronate OR Etidronate OR Clodronate) (85.294).

TÓPICO: (Osteonecroses OR Bone Necrosis OR Necrosis, Avascular, of Bone OR Avascular Necrosis of Bone OR Bone Avascular Necrosis OR Necrosis, Aseptic, of Bone OR Aseptic Necrosis of Bone OR Bone Aseptic Necrosis OR Bone Necroses OR Necroses, Bone OR Kienbock Disease OR Kienbock's Disease OR Kienboeck Disease OR Kienboeck's Disease OR Kienboecks Disease) (26.369).

3 # 2 AND #1 – (1.041)

Quadro 9 - Search strategy used at BVS

(Bisphosphonate Associated Osteonecrosis of the Jaw OR Alendronate OR Zoledronic Acid OR Everolimus OR Lenalidomide OR Pazopanib OR Ramucirumab OR Thalidomide OR Olpadronate OR Etidronate OR Clodronate Bevacizumab OR Denosumab OR Ibandronate OR Neridronate OR Pamidronate OR Residronate OR Sirolimus OR Sorafenib OR Sunitinib OR Tiludronic acid OR Zoledronic Acid OR Everolimus OR Lenalidomide OR Pazopanib OR Ramucirumab OR Thalidomide OR Olpadronate OR Etidronate OR Clodronate) AND (Osteonecroses OR Bone Necrosis OR Necrosis, Avascular, of Bone OR Avascular Necrosis of Bone OR Bone Necrosis OR Necrosis, Aseptic, of Bone OR Aseptic Necrosis of Bone OR Bone Necroses OR Necroses, Bone OR Kienbock Disease OR Kienbock's Disease OR Kienboeck Disease OR Kienboecks Disease) (300).

Quadro 10 - Search strategy used at CAPES

Biblioteca Nacional Brasileira de Teses e Dissertações

<http://bdtd.ibict.br/vufind/Search/Results?lookfor=Osteonecrose+Maxila+Mandibula+&type>AllFields>

Osteonecrose Maxila Mandibula (19)

Quadro 11 - Search strategy used at SCOPUS

Osteonecroses OR Bone Necrosis OR Necrosis, Avascular, of Bone OR Avascular Necrosis of Bone OR Bone Avascular Necrosis OR Necrosis, Aseptic, of Bone OR Aseptic Necrosis of Bone OR Bone Aseptic Necrosis OR Bone Necroses OR Necroses, Bone OR Kienbock Disease OR Kienbock's Disease OR Kienboeck Disease OR Kienboeck's Disease OR Kienboecks Disease AND Bisphosphonate Associated Osteonecrosis of the Jaw OR Alendronate OR Bevacizumab OR Denosumab OR Ibandronate OR Neridronate OR Pamidronate OR Residronate OR Sirolimus OR Sorafenib OR Sunitinib OR Tiludronic acid OR Zoledronic Acid OR Everolimus OR Lenalidomide OR Pazopanib OR Ramucirumab OR Thalidomide OR Olpadronate OR Etidronate OR Clodronate Bisphosphonate Associated Osteonecrosis of the Jaw OR Alendronate OR Bevacizumab OR Denosumab OR Ibandronate OR Neridronate OR Pamidronate OR Residronate OR Sirolimus OR Sorafenib OR Sunitinib OR Tiludronic acid OR Zoledronic Acid OR Everolimus OR Lenalidomide OR Pazopanib OR Ramucirumab OR Thalidomide OR Olpadronate OR Etidronate OR Clodronate (126).
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APPENDIX C. LIST OF EXCLUDED STUDIES (N= 50)

STUDY	REASON EXCLUSION
AGRILLO A; NASTRO SE; FACCHINI A; FILIACI F; UNGARI C. Osteonecrosis of the jaws in patients assuming bisphosphonates and sunitinib: two case reports. European Review for Medical and Pharmacological Sciences , v. 16, n. 7, p. 952–957, 2012.	Study design
AL-SABBAGH M; ROBINSON FG; ROMANOS G; THOMAS MV. Osteoporosis and bisphosphonate-related osteonecrosis in a dental school implant patient population. Implant Dentistry , v. 24, n. 3, p. 328–332, 2015.	No procedure dental
ALBU S; DINU C. Osteonecrosis of the maxilla associated with the use of bisphosphonates. Otolaryngology - Head and Neck Surgery , v. 143, n. 6, p. 847–848, 2010.	Study design
ALBU S. Bisphosphonates and osteonecrosis of the maxilla. QJM , v. 107, n. 4, p. 311, 2014.	Study design
ALLEGRA A; OTERI G; NASTRO E; ALONCI A; BELLOMO G; DEL FABRO V; QUARTARONE E; ALATI C; DE PONTE FS; CICCIU D; MUSOLINO C. Patients with bisphosphonates-associated osteonecrosis of the jaw have reduced circulating endothelial cells. Hematological Oncology , v. 25, n. 4, p. 164–169, 2007.	No procedure dental
ALLEN MR; BURR DB. The Pathogenesis of Bisphosphonate-Related Osteonecrosis of the Jaw: So Many Hypotheses, So Few Data. Journal of Oral and Maxillofacial Surgery , v. 67, n. 5, p. 61–70, 2009.	Study design
ALLEN MR. Bisphosphonates and osteonecrosis of the jaw: moving from the bedside to the bench. Cells Tissues Organs , v. 189, n. 1–4, p. 289–294, 2008.	Study design
ALLEN MR; RUGGIERO SL. A review of pharmaceutical agents and oral bone health: how osteonecrosis of the jaw has affected the field. The International Journal of Oral & Maxillofacial Implants , v. 29, n. 1, p. e45–e57, 2014.	Study design
ALMĂSAN HA; BĂCIUT M; ROTARU H; BRAN S; ALMĂSAN OC; BĂCIUT G. Osteonecrosis of the jaws associated with the use of bisphosphonates. Discussion over 52 cases. Romanian Journal of Morphology and Embryology , v. 52, n. 4, p. 1233–1241, 2011.	No procedure dental
ALTUNDAG K; BULUT NDN; TEZCAN MDE; OZEN MDM; PURNAK MDT. Tooth extraction: Is it inciting event or sequela of osteonecrosis of the jaws associated with intravenous bisphosphonates? Journal of Oral and Maxillofacial Surgery , v. 65, n. 1, p. 154, 2007.	Other population
ALTUNDAG K. Medication-related osteonecrosis of the jaw incidence in patients exposed concomitantly to bone resorption inhibitors and vascular endothelial growth factor receptor tyrosine kinase inhibitors: is it generalizable to all solid tumors? Supportive Care in Cancer , v. 27, n. 6, p. 1961, 2019.	Other population
AUZINA D; SLAIDINA A; SEVAST JM; ERTS R; LEJNIEKS A; LEJNIECE SA population based study of multiple myeloma patients with medication-related osteonecrosis of the jaw. Stomatologija, Baltic Dental and Maxillofacial Journal , v. 21, n. 1, p. 13–17, 2019.	No procedure dental
BADEL T; KEROS J; KRAPAC L; Pavičin I. Povezanost osteonekroze celjusti i terapije bisfosfonatima. Arhiv za Higijenu Rada i Toksikologiju , v. 61, n. 3, p. 371–380, 2010.	Study design
BAGAN JV; JIMENEZ Y; MURILLO J; HERNANDEZ S; POVEDA R; SANCHIS JM; DIAZ JM; SCULLY C. Jaw osteonecrosis associated with bisphosphonates: Multiple exposed areas and its relationship to teeth extractions. Study of 20 cases. Oral Oncology , v. 42, n. 3, p. 327–329, 2006.	Other population
BAMIAS A; KASTRITIS E; BAMIA C; MOULOPOULOS LA; MELAKOPOULOS I; BOZAS G; KOUTSOUKOU V; GIKA D; ANAGNOSTOPOULOS A; PAPADIMITRIOU C; TERPOS E; DIMOPOULOS MA. Osteonecrosis of the jaw in cancer after treatment	No procedure dental

with bisphosphonates: Incidence and risk factors. Journal of Clinical Oncology , v. 23, n. 34, p. 8580–8587, 2005.	
BROZOSKI MA; TRAINA AA; CRISTINA M; DEBONI Z. Bisphosphonate-related osteonecrosis of the jaw. Revista Brasileira de Reumatologia , v. 52, n. 2, p. 260–270, 2012.	Study design
BUJANDA DA; CABRERA S; MIGUEL A; SARMIENTO UB; PÉREZ SQ; MORALES JA. Osteonecrosis of the jaws in patients with bone metastasis receiving intravenous bisphosphonates. A rising concern. Clinical and Translational Oncology , v. 8, n. 12, p. 919–921, 2006.	Study design
CHENG A; HUTCHESON A; SAMBROOK P; GOSS A. The frequency of bisphosphonate related osteonecrosis of the jaws (BRONJ): a single centre prospective. International Journal of Oral and Maxillofacial Surgery , v. 42, n. 10, p. 1185, 2013.	Other population
COMPSTON J. Oral bisphosphonates and osteonecrosis of the jaw: are the mhra recommendations appropriate? Menopause International , v. 13, n. 2, p. 54–55, 2007.	Study design
FUJIEDA Y; DOI M; ASAKA T; OTA M; HISADA R; OHNISHI N; KONO M; KAMEDA H; NAKAZAWA D; KATO M; AMENGUAL O; TAKAHATA M; YASUDA S; KITAGAWA Y; ATSUMI T. Incidence and risk of anti-resorptive agent-related osteonecrosis of the jaw (ARONJ) after tooth extraction in patients with autoimmune disease. Journal of Bone and Mineral Metabolism , v. 38, p. 581–588, 2020.	Therapy combined or other anti-resorptive drug
FURTADO IA; FRANCO CC; LANÇA F; SILVA SF. Anatomic factors related to bisphosphonate osteonecrosis of the jaws: A Portuguese retrospective study. Acta Medica Portuguesa , v. 25, n. 2, p. 106–110, 2012.	Other population
GALIS B; ZAJKO J; HIRJAK D; VANKO L; KUPCOVA I; JURKEMIK J; GENGELOVA P; MIKUSKOVA K; HALMOVA K; RIZNIC M; CZAKO L. Is the prevalence of the medication-related osteonecrosis of the jaws underestimated, evaluation in oncological and non- -oncological disease. Bratislava Medical Journal , v. 118, n. 12, p. 724 – 731, 2017.	No procedure dental
GRBIC JT; LANDESBERG R; LIN SQ; MESENBRINK P; REID IR; LEUNG PC; CASAS N; RECKNOR CP; HUA Y; DELMAS PD; ERIKSEN EF. Incidence of osteonecrosis of the jaw in women with postmenopausal osteoporosis in the health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial. Journal of the American Dental Association , v. 139, n. 1, p. 32–40, 2008.	No procedure dental
GOSS A; BARTOLD M; SAMBROOK P; HAWKER P. The Nature and Frequency of Bisphosphonate-Associated Osteonecrosis of the Jaws in Dental Implant Patients: A South Australian Case Series. Journal of Oral and Maxillofacial Surgery , v. 68, n. 2, p. 337-343, 2010.	Other population
HOLZINGER D; SEEMANN R; MATONI N; EWERS R; MILLESI W; WUTZL A. Effect of dental implants on bisphosphonate-related osteonecrosis of the jaws. Journal of Oral and Maxillofacial Surgery , v. 72, n. 10, p. 1937.e1-1937.e8, 2014.	Other population
HASEGAWA T; HAYASHIDA S; KONDO E; TAKEDA Y; MIYAMOTO H; KAWAOKA Y; UEDA N; IWATA E; NAKAHARA H; KOBAYASHI M; SOUTOME S; YAMADA S; TOJOYI I; KOJIMA Y; UMEDA M; FUJITA S; KURITA H; SHIBUYA Y; KIRITA T; KOMORI T. Japanese Study Group of Co-operative Dentistry with Medicine (JCDM). Medication-related osteonecrosis of the jaw after tooth extraction in cancer patients: a multicenter retrospective study. Osteoporosis International , V. 30, p. 231–239, 2019.	Therapy combined or other anti-resorptive drug
JACOBSEN C; METZLER P; RÖSSLER M; OBWEGESER J; ZEMANN W; GRÄTZ K W. Osteopathology induced by bisphosphonates and dental implants: Clinical observations. Clinical Oral Investigations , v. 17, n. 1, p. 167-175, 2013.	Other population
KYRGIDIS A; VAHTSEVANOS K. Osteonecrosis of the jaw in patients receiving oral bisphosphonates. Osteoporosis International , v. 21, n. 3, p. 535–536, 2010.	Study design

KOS M. Incidence and risk predictors for osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. Archives of Medical Science , v. 11, n. 2, p. 319–324, 2015.	No procedure dental
KWON TG; LEE CO; PARK JW; CHOI SY; RIJAL G; SHIN HI. Osteonecrosis associated with dental implants in patients undergoing bisphosphonate treatment. Clinical Oral Implants Research , v. 25, n. 5 p. 632-640, 2014.	Other population
LO JC; O'RYAN FS; GORDON NP; YANG J; HUI RL; MARTIN D; HUTCHINSON M; LATHON PV; SANCHEZ G; SILVER P; CHANDRA M; MCCLOSKEY CA; STAFFA JA; WILLY M; SELBY JV; GO AS. Prevalence of Osteonecrosis of the Jaw in Patients With Oral Bisphosphonate Exposure. Journal of Oral and Maxillofacial Surgery , v. 68, n. 2, p. 243–253, 2010.	No procedure dental
MAST G; OTTO S; MÜCKE T; SCHREYER C; BISSINGER O; KOLK A; WOLFF KD; EHRENFEILD M; STÜRZENBAUM SR; PAUTKE C. Incidence of maxillary sinusitis and oro-antral fistulae in bisphosphonate-related osteonecrosis of the jaw. Journal of Cranio-Maxillofacial Surgery , v. 40, n. 7, p. 568–571, 2012.	No procedure dental
MANFREDI M; MERIGO E; GUIDOTTI R; MELETI M; VESCOVI P. Bisphosphonate-related osteonecrosis of the jaws: a case series of 25 patients affected by osteoporosis. International Journal of Oral and Maxillofacial Surgery , v. 40, n. 3, p. 277-284, 2011.	Other population
OWOSHOO AA; LIANG STY; SAX AZ; WU K; YOM SHK; HURYN JM; ESTILO CL. Medication-related osteonecrosis of the jaw: An update on the memorial sloan kettering cancer center experience and the role of premedication dental evaluation in prevention. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology , v. 125, n. 5, p. 440–445, 2018.	Other population
PETTROVIC M; JELOVAC DB; ANTIC S; ANTUNOVIC M; LUKIC N; SABANI M; MUDRAK J; JEZDIC Z; PUCAR A; STEFANOVIĆ A; KUZMANOVIC C; NIKOLIC D; KONSTANTINOVIĆ V. Medication-related osteonecrosis of the jaws: two center retrospective cohort studies. Biomed research international , v. 2019, n. 1, p. 1-10, 2019.	Therapy combined or other anti-resorptive drug
RAISSOUNI AT; MOYA EP; RAMOS ME; MARTÍNEZ DVTMD; SANZ VS; ORTEGA LSJ. Bisphosphonate-induced osteonecrosis of the jaw in a patient with metastatic breast cancer. Revista Espana de Medicina Nuclear , v. 30, n. 5, p. 322–323, 2011.	Study design
RIBEIRO GH; CHRUN ES; DUTRA KL; DANIEL FI; GRANDO LJ. Osteonecrosis of the jaws: a review and update in etiology and treatment. Brazilian Journal of Otorhinolaryngology , v. 84, n. 1, p. 102–108, 2018.	Study design
RUGGIERO SL. Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ): Initial Discovery and Subsequent Development. Journal of Oral and Maxillofacial Surgery , v. 67, n. 5, p. 13–18, 2009.	No procedure dental
SANTOS M; SILVEIRA K; SOUZA N; COSTA DIS. Extensive osteonecrosis of the maxilla caused by bisphosphonates: Report of a rare case. Journal of Clinical and Experimental Dentistry , v. 11, n. 2, p. e203–e207, 2019.	Study design
SCIANNAMEO V; MATTEINI C; PERUGINI M; Di Curzio P; SAPONARO GTC. Bisphosphonate-related osteonecrosis of the jaw: A retrospective study on the role of dental prophylaxis. European Journal of Inflammation , v. 11, n. 3, p. 901–906, 2013.	No procedure dental
SHAH NP; KATSARELIS H; PAZIANAS M; DHARIWAL DK. Periodontal disease, dental implants, extractions and medications related to osteonecrosis of the jaws. Dental Update , v. 42, n. 9, p. 878–889, 2015.	Study design
THUMBIGERE-MATH V; TU L; HUCKABAY S; DUDEK AZ; LUNOS S; BASI DL; HUGHES PJ; LEACH JW; SWENSON KK; GOPALAKRISHNAN R. A retrospective study evaluating frequency and risk factors of osteonecrosis of the jaw in 576 cancer	No procedure dental

patients receiving intravenous bisphosphonates. American Journal of Clinical Oncology: Cancer Clinical Trials , v. 35, n. 4, p. 386–392, 2012.	
VAHTSEVANOS K; KYRGIDIS A; VERROU E; KATODRITOU E; TRIARIDIS S; ANDREADIS CG; BOUKOVINAS I; KOLOUTSOS GE; TELEIOUDIS Z; KITIKIDOU K; PARASKEVOPOULOS P; ZERVAS K; ANTONIADES K. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. Journal of Clinical Oncology , v. 27, n. 32, p. 5356–5362, 2009.	No procedure dental
WALTER C; GRÖTZ KA; KUNKEL M; AL-NAWAS B. Prevalence of bisphosphonate associated osteonecrosis of the jaw within the field of osteonecrosis. Supportive Care in Cancer , v. 15, n. 2, p. 197–202, 2007.	Therapy combined or other anti-resorptive drug
WALTER C; SAGHEB K; BITZER J; RAHIMI-NEDJAT R; TAYLOR KJ. Analysis of reasons for osteonecrosis of the jaws. Clinical Oral Investigations , v. 18, n. 9, p. 2221–2226, 2014.	Therapy combined or other anti-resorptive drug
WANG THMD; CHIA-JEN LMD; TZE-FAN CHAO MD; TZENG-JI CHEN MD; YU-WEN HU MD. Risk factors for and the role of dental extractions in osteoradionecrosis of the jaws: A national-based cohort study. Head & Neck , p. 1-9, 2017.	Therapy combined or other anti-resorptive drug
WALTER C; LAUX C; SAGHEB K. Radiologic bone loss in patients with bisphosphonate-associated osteonecrosis of the jaws: A case-control study. Clinical Oral Investigations , v. 18, n. 2, p. 385–390, 2014.	No procedure dental
WAZZAN T; KASHTWARI D; ALMADEN WF; GONG Y; CHEN Y; MOREB J; KATZ J. Radiographic bone loss and the risk of medication-related osteonecrosis of the jaw (MRONJ) in multiple myeloma patients—A retrospective case control study. Special Care in Dentistry , v. 38, n. 6, p. 356–361, 2018.	No procedure dental
WILDE F; HENDRICKS J; RIESE C; PAUSCH NC; SCHRAMM A; HEUFELDER M. Bone regeneration without bone grafting after resection of a segment of the mandible to treat bisphosphonate-related osteonecrosis of the jaw. Journal of Oral and Maxillofacial Surgery , v. 69, n. 10, p. 2657–2662, 2011.	Study design
WUTZL A; BIEDERMANN E; WANSCHITZ F; SEEMANN R; KLUG K; BAUMANN A; WATZINGER F; SCHICHO K; EWERS R; MILLESI G. Treatment results of bisphosphonate-related osteonecrosis of the jaw. Head & Neck , p. 1224–1230, 2008.	No procedure dental
YAMADA SI; HAYASHIDA S; YANAMOTO S; NARUSE T; MATSUSITA Y; UDA A; ROKUTANDA S; KAKEHASHI H; IKEDA H; ASAHIKA I; UMEDA M. A new strategy for surgical intervention of bisphosphonate-related osteonecrosis of the jaw: A retrospective study. Acta Médica Nagasakiensia , v. 60, n. 3, p. 97–102, 2016.	No procedure dental
ZAVRAS AI; ZHU S. Bisphosphonates Are Associated With Increased Risk for Jaw Surgery in Medical Claims Data: Is it Osteonecrosis? Journal of Oral and Maxillofacial Surgery , v. 64, n. 6, p. 917–923, 2006.	No procedure dental

APPENDIX D. LIST OF INCLUDED STUDIES (N= 27)

STUDY
ALZOMAN H.A. Prevalence of jaw osteonecrosis among patients receiving bisphosphonates in Riyadh. King Saud University Journal of Dental Sciences , v. 2, p. 29–32, 2011.
GRANT B.T; AMENEDO C; FREEMAN K; KRAUT R.A. Outcomes of placing dental implants in patients taking oral bisphosphonates: A review of 115 cases. Journal Oral Maxillofacial. Surgical , v. 66, p.223-230, 2008.
FERLITO S; PUZZO S; LIARDO C. Preventive protocol for tooth extractions in patients treated with zoledronate: A case series. Journal Oral Maxillofacial. Surgical , v.69, p.1-4, 2011.
FUGAZZOTTO PA, LIGHTFOOT WS, JAFFIN R, KUMAR A. Implant Placement With or Without Simultaneous Tooth Extraction in Patients Taking Oral Bisphosphonates: Postoperative Healing, Early Follow-Up, and the Incidence of Complications in Two Private Practices. Journal Periodontology , v. 78, n. 9, p. 1664–9, 2007.
HASEGAWA T; RI S; UMEDA M; KOMATSUBARA H; KOBAYASHI M; SHIGETA T; YOSHITOMI I; IKEDA H; SHIBUYA I; ASAHIKA I; KOMORI T. The observational study of delayed wound healing after tooth extraction in patients receiving oral bisphosphonate therapy. Journal of Cranio-Maxillo-Facial Surgery , v 41, p. 558-563, 2013.
HUTCHESON A; CHENG A; KUNCHAR R; STEIN B; SAMBROOK P; GOSS A.A. C-Terminal crosslinking telopeptide test-based protocol for patients on oral bisphosphonates requiring extraction: A prospective single-center controlled study. Journal Oral Maxillofacial. Surgical , v. 72, i. 8, p.1456-1462, 2014.
KANG S.H; PARK S.J; KIM M.K. The effect of bisphosphonate discontinuation on the incidence of postoperative medication-related osteonecrosis of the jaw after tooth extraction. Journal Korean Associacion Oral Maxillofacial Surgical , v. 46, no. p. 78-83, 2020.
KOKA S, BABU N.M.S, NORELL A. Survival of dental implants in post-menopausal bisphosphonate users. Journal Prosthodontic Research , v. 54, n. 3, n. 108–11, 2010.
LAZAROVICI T.S; MESILATY-GROSS S; VERED I; PARIENTE C; KANET H; GIVOL N; YAHALOM R; TAICHER S; YAROM N. Serologic bone markers for predicting development of osteonecrosis of the jaw in patients receiving bisphosphonates. Journal Oral Maxillofacial. Surgical , v. 68, p. 2241-2247, 2010.
LODI G; SARDELLA A; SALIS A; DEMAROSI F; TAROZZI M; CARRASSI A. Tooth Extraction in Patients Taking Intravenous Bisphosphonates: A Preventive Protocol and Case Series. Journal Oral Maxillofacial. Surgical , v. 68, p. 107-110, 2010.
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