UNIVERSIDADE FEDERAL DO PARANÁ

ROBERTA SCHRODER ROCHA

POLIMORFISMOS EM METALOPROTEASES COMO FATOR DE RISCO NA OSSEOINTEGRAÇÃO E AVALIAÇÃO DE SINUSITE COMO EFEITO ADVERSO APÓS REALIZAÇÃO DE LEVANTAMENTO DE SEIO E INSTALAÇÃO DE IMPLANTES ZIGOMÁTICOS

CURITIBA

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Tese apresentada ao curso de Pós-Graduação em Biologia Celular e Molecular, Setor de Ciências Biológicas, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Doutor em Biologia Celular e Molecular.

Orientadora: Profa. Dra. Maria Cristina Leme Godoy dos Santos

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Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação BIOLOGIA CELULAR E MOLECULAR da Universidade Federal do Paraná foram convocados para realizar a arguição da tese de Doutorado de **ROBERTA SCHRODER ROCHA** intitulada: **POLIMORFISMOS EM METALOPROTEASES COMO FATOR DE RISCO NA OSSEOINTEGRAÇÃO E AVALIAÇÃO DE SINUSITE COMO EFEITO ADVERSO APÓS REALIZAÇÃO DE LEVANTAMENTO DE SEIO E INSTALAÇÃO DE IMPLANTES ZIGOMÁTICOS**, sob orientação do Prof. Dr. MARIA CRISTINA LEME GODOY DOS SANTOS, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

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Dedico essa tese a todos que de alguma forma me ajudaram ou torceram pelas minhas conquistas durante toda minha vida.

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“Só fazemos melhor aquilo que repetidamente insistimos em melhorar. A busca da excelência não deve ser um objetivo, e sim um hábito”. (ARISTÓTELES)

RESUMO

Devido ao aumento da expectativa de vida, é visto cada vez mais doenças ósseas na população e uma das terapêuticas utilizadas para melhorar a qualidade de vida desses pacientes é a instalação de implantes osseointegrados. Apesar da osseointegração de implantes apresentar resultados previsíveis, reproduzíveis e estáveis ao longo do tempo, garantindo um alto índice de sucesso, falhas e complicações ainda ocorrem. O objetivo desse estudo foi avaliar, por meio de duas revisões sistemática e metanálise, os polimorfismos em metaloproteases como fator de risco na osseointegração e a sinusite como efeito adverso após realização de levantamento de seio e instalação de implantes zigomáticos. Ambas as metanálises foram registradas no PROSPERO. Títulos e resumos foram selecionados em diferentes bases de dados, e os artigos analisados completamente em relação aos critérios de inclusão e exclusão. Ferramentas validadas foram usadas para avaliar a qualidade e o risco de viés dos estudos incluídos. Análises estatísticas foram realizadas para avaliar o desfecho. Com relação à associação de polimorfismos de metaloproteases e falha de osseointegração, concluiu-se que o polimorfismo MMP-1 g.-1607 G>GG (rs1799750) foi estatisticamente associado à falha na osseointegração como fator protetor. O MMP-8 g.-799 C>T (rs11225395) foi associado a um maior risco de falha na osseointegração do implante. O MMP-1 g. 3' UTR C>T (rs5854) foi associado a um maior risco de falha do implante na população caucasiana, enquanto na população asiática é um fator protetor. Por fim, a MMP-3 g.-1612 5A>6A (rs3025058) e a MMP-1 g.-519 A>G (rs1144393) pareceram não apresentaram associação com falha na osseointegração isoladamente. Já com relação à sinusite, demonstrou-se que a prevalência combinada de sinusite após a instalação do implante zigomático foi de 3,76%, e após o procedimento de levamento de seio foi de 1,11%. Na análise de subgrupo, a maior prevalência de sinusite para instalação de implantes zigomático foi a técnica de slot (21,62%) e para o levantamento de seio a abordagem da janela lateral (1,35%). Dessa forma, o estudo contribuiu para uma melhor compreensão das complicações durante e após a osseointegração.

Palavras-chave: Sinusite. Levantamento de Seio. Implante Zigomático. Metaloprotease. Polimorfismo genético.

ABSTRACT

Due to the increase in life expectancy, bone diseases are seen more in the population and one of the therapies used to improve the quality of life of these patients is the placement of osseointegrated implants. Despite the osseointegration of implants presenting predictable, reproducible and stable results over time, ensuring a high success rate, failures and complications still occur. Therefore, the objective of this study was to evaluate, through two systematic reviews and meta-analysis, the polymorphisms in metalloproteases as risk factors for osseointegration and sinusitis as adverse event after sinus lift procedure and zygomatic implant placement. Both meta-analyses were registered in PROSPERO. Titles and abstracts were searched in different databases and the articles were fully analyzed in relation of inclusion and exclusion criteria. Validated tools were used to assess the quality and risk of bias of the included studies. Statistical analyzes were performed to evaluate the outcome. Regarding the association of metalloprotease polymorphisms and osseointegration failure, it was concluded that the polymorphism MMP-1 g.-1607 G>GG (rs1799750) was statistically associated with failure in osseointegration as a protective factor. MMP-8 g.-799 C>T (rs11225395) was associated with an increased risk of implant osseointegration failure. MMP-1 g. 3' UTR C>T (rs5854) was associated with a higher risk of implant failure in the Caucasian population, whereas in the Asian population it is a protective factor. Finally, MMP-3 g.-1612 5A>6A (rs3025058) and MMP-1 g.-519 A>G (rs1144393) did not appear to be associated with failure in osseointegration. Regarding the sinusitis, it was showed that the prevalence of sinusitis after the installation of the zygomatic implant was 3.76%, and after the sinus lift procedure it was 1.11%. In the subgroup analysis, the highest prevalence of sinusitis for the installation of zygomatic implants was the slot technique (21.62%) and for sinus lift the lateral window approach (1.35%). In this way, the study contribuited to a better understanding of complications during and after osseointegration.

Keywords: Sinusitis. Sinus Lift. Zygomatic Implant. Metalloproteinase. Genetic Polimorfism.

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LISTA DE ABREVIATURAS OU SIGLAS

MEC	- Matriz Extracelular
MMP	- Matriz Metaloprotease
SNP	- Polimorfismo de Nucleotídeo Único
IGF	- Fator de Crescimento Semelhante à Insulina Tipo 1
TGF-β	- Fator De Transformação Do Crescimento - beta
FGF	- Fator De Crescimento De Fibroblasto
EGF	- Fator de Crescimento Epidermal
BMP	- Proteína Morfogenética Óssea
PTH	- Paratormônio
IL	- Interleucina
PGE	- Prostaglandina
TNF	- Fator de Necrose Tumoral
M-CSF	- Fator De Estimulação De Colônia De Macrófagos
GM-CSF	- Fator Estimulador De Colônias Granulocitárias
PDGF	- Fator De Crescimento Derivado De Plaquetas
OPG	- Osteoprotegerina

SUMÁRIO

1 INTRODUÇÃO

Com o aumento da expectativa de vida, tem sido visto um rápido crescimento de doenças ósseas, que podem acarretar graves problemas biológicos, funcionais e psicológicos aos pacientes. Uma das terapêuticas utilizada para melhorar a qualidade de vida desses pacientes é a instalação de implantes osseointegrados, que passam a exercer a função anteriormente desempenhada por determinadas partes do corpo, tendo função estrutural e de suporte mecânico. A utilização de implantes com esse fim tem sido bastante difundida na área de saúde.

Apesar da osseointegração de implantes apresentar resultados previsíveis, reproduzíveis e estáveis ao longo do tempo, garantindo um alto índice de sucesso, falhas e complicações ainda ocorrem. Além disso, devido à sua ampla utilização em todo o mundo, torna-se cada vez mais frequente a ocorrência de falhas de implantes e complicações relacionadas, como a sinusite pós-operatória.

Sabe-se que os fatores relacionados ao hospedeiro podem ser a chave para a compreensão dos processos que levam a diferentes falhas na osseointegração e suas complicações. Entre esses fatores está o equilíbrio da atividade das metaloproteases da matriz (MMPs).

As MMPs são enzimas endopeptidases secretadas de forma altamente regulada pelas células locais, capazes de degradar praticamente toda a matriz extracelular e seus componentes. Suas atividades biológicas influenciam criticamente o comportamento celular, as vias de sinalização e o sistema imune devido à diversidade de alvos de degradação e às suas atividades proteolíticas. O desequilíbrio dessas enzimas pode comprometer o processo de osseointegração (CAUWE; VAN DEN STEEN; OPDENAKKER, 2007; ITOH; SEIKI, 2006; PAIVA; GRANJEIRO, 2014).

A literatura demonstra que diversos fatores podem estar associados à falha de implantes osseointegrados. Entretanto, um pequeno número de perdas ocorre sem causas clinicamente reconhecidas, sugerindo que fatores intrínsecos ao hospedeiro desempenham um papel importante na sobrevivência dos implantes osseointegrados. Além disso, parece existir indivíduos com maior suscetibilidade à perda de implantes, e essa predisposição pode ser explicada por diferenças genéticas, como os polimorfismos (DEL VALLE et al., 2018).

Polimorfismos são pequenas variações genéticas em que um ou mais alelos têm frequência gênica maior que 1% (NUSSBAUM; MCINNES; WILLARD, 2015). Alguns polimorfismos afetam os níveis de expressão gênica e a produção ou funções de proteínas, influenciando diversas patologias. Polimorfismos em genes de MMPs já foram associados à perda de implantes osseointegrados (SANTOS et al., 2004).

A literatura descreve algumas complicações após a instalação de implantes osseointegrados. Entre elas, destaca-se a sinusite, uma inflamação dos seios paranasais que afeta as membranas e mucosas que revestem o nariz e os seios faciais, como uma das complicações mais frequentes após instalação de implantes zigomáticos, utilizados para tratar pacientes edêntulos com atrofia alveolar severa da maxila e após a realização de técnicas adjuvantes como o levantamento de seio (CHEN et al., 2013; KIM et al., 2019; KIM; HWANG; YUN, 2013).

A realização de revisões sistemáticas e metanálises visando identificar polimorfismos em metaloproteases como fator de risco na osseointegração e avaliação de sinusite como efeito adverso após realização de levantamento de seio e instalação de implantes zigomáticos pode contribuir com uma melhor compreensão do complexo processo de osseointegração e seus fatores de risco individuais.

1.1 JUSTIFICATIVA

Com a popularização da implantodontia e os avanços recentes, cada vez mais pacientes fazem uso dessa terapia hoje no mundo. Com o aumento do uso, complicações que antes não eram tão comuns, são mais frequentemente relatadas. As complicações dependem de vários fatores e devem ser avaliadas durante o planejamento do tratamento do paciente.

Desta forma, assim como em outras áreas, o desafio atual da implantodontia está na habilidade em detectar pacientes de risco e desenvolver estratégias individualizadas de terapia. Estratégias individualizadas de terapia vêm ganhando espaço na oncologia e farmacologia, mas ainda carece de conhecimento na área de implantes osseointegráveis o que coloca esse trabalho na contribuição do desbravamento dessa área.

Dessa maneira, uma melhor compreensão dos polimorfismos envolvidos na falha de osseointegração e da incidência de sinusite, pode ajudar no direcionamento de um tratamento individualizado e mais eficaz.

1.2 OBJETIVOS

1.2.1 Objetivo geral

Avaliar polimorfismos em metaloproteases como fatores de risco genético a falha na osseointegração, e sinusite como complicação dos tratamentos com implantes osseointegrados.

1.2.2 Objetivos específicos

- Identificar por meio de revisão sistemática e metanálise os principais polimorfismos em metaloproteases envolvidos na falha de osseointegração;
- Avaliar, por meio de revisão sistemática e metanálise, a frequência de ocorrência de sinusite após cirurgia para instalação de implantes zigomáticos e procedimento de levantamento de seio.

2 REVISÃO DE LITERATURA

2.1 TECIDO ÓSSEO

2.1.1 Estrutura e organização

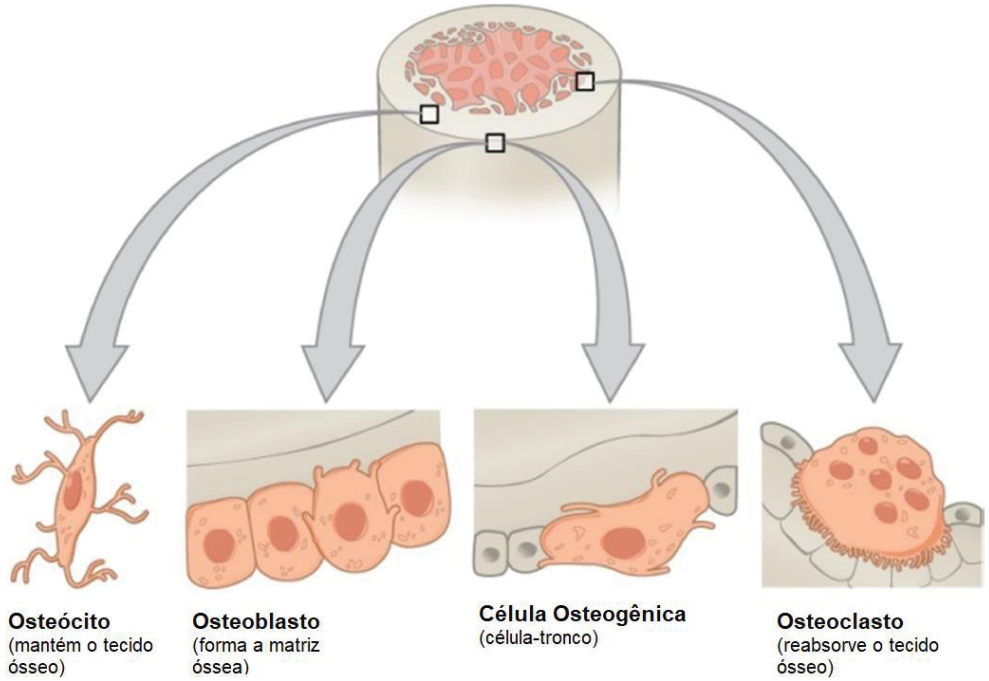
O tecido ósseo desempenha diversas funções no organismo, dentre elas funções mecânica, sintética e metabólica. O osso é importante para a proteção, locomoção, movimento, ponto de inserção para os músculos, ligamentos e tendões, suporte mecânico e arcabouço para os tecidos mais importantes. Adicionalmente, uma estrutura do osso chamada medula óssea, é responsável pela hematopoiese e contém minerais vitais para o funcionamento do corpo humano (ANSARI, 2019).

O osso não é homogeneamente sólido, sendo composto de células ósseas vivas e uma matriz mineralizada. O tecido ósseo é formado de 30% de material orgânico e 70% de material inorgânico. Dos 30% orgânico, 90% são compostos de fibras de colágeno, principalmente colágeno tipo I e o outro 10% de proteínas não colagenosas, além de lipídeos e proteoglicanos. A parte inorgânica é formada principalmente por cristais de fosfato de cálcio na forma de hidroxiapatita (ANSARI, 2019; PERIĆ KAČAREVIĆ et al., 2020).

Existem dois tipos principais de osso, o cortical e o trabecular ou esponjoso, que apesar de exibir os mesmos componentes, apresentam uma diferença estrutural, onde o osso cortical é compacto e tem uma porosidade entre 5 e 30% e uma resistência à compressão de 100-200 Megapascal. Já o osso trabecular tem uma porosidade entre 30 e 90% e uma menor resistência à compressão de 2-12 MPa (PERIĆ KAČAREVIĆ et al., 2020). Ambos os tipos estão presentes em todas as peças ósseas, sendo, porém, sua proporção dependente da localização do osso.

Quatro tipos principais de células são encontrados no tecido ósseo, são elas: células osteogênicas, osteoblastos, osteoclastos e osteócitos (FIGURA 1).

FIGURA 1 – OS QUATRO TIPOS DE CÉLULAS MAIS IMPORTANTES ENCONTRADAS NO TECIDO ÓSSEO



FONTE: (ANSARI, 2019).

As células osteogênicas são derivadas das células-tronco mesenquimatosas e são encontradas nas superfícies e canais ósseos, e na microvascularização óssea. No adulto são células achatadas, com núcleo pequeno e citoplasma escasso, indicando uma célula em repouso. Tornam-se ativas quando estimuladas por fatores de transcrição, como fator de ligação central alfa-1, fator de transcrição relacionado 2, proteínas morfogenéticas ósseas (BMP), ou ainda quando estimuladas por campo eletromagnético pulsado (ANSARI, 2019).

Dessa forma originam os osteoblastos, célula responsável pelo desenvolvimento e remodelação óssea. Os osteoblastos são células que sintetizam a parte orgânica da matriz extracelular óssea, produzindo uma mistura proteica chamada osteóide (ANSARI, 2019), que posteriormente será mineralizada, pela adição de fosfato de cálcio.

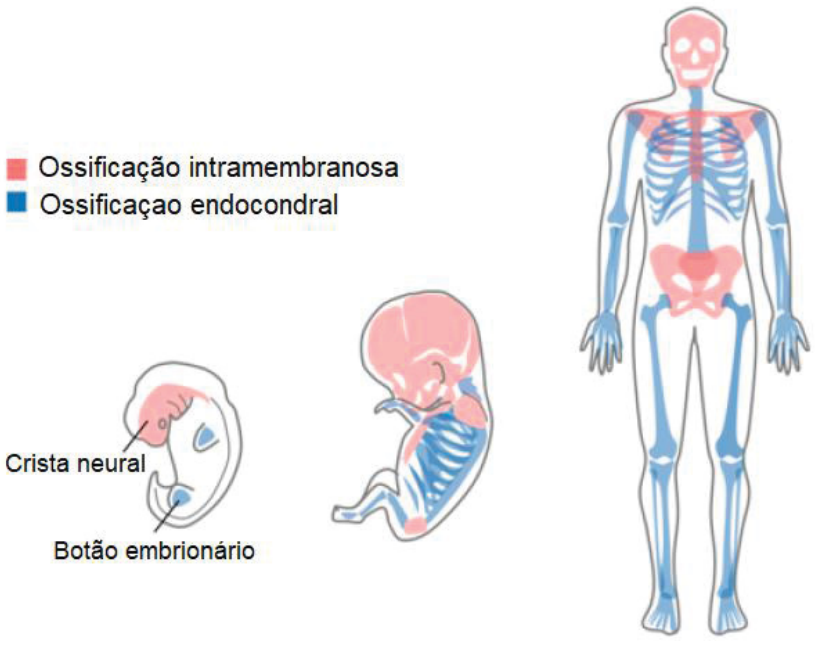
Os osteócitos são osteoblastos inativos ou menos ativo presos pela própria matriz mineralizada. Apesar da menor atividade, mantem a conexão entre as células ósseas e com a vascularização, tendo importante papel de comunicação entre as células do tecido. Devido a este papel, está envolvido em diversas cascatas de

sinalizações bioquímicas, contribuindo para a regulação da homeostase de cálcio e fosfato (ANSARI, 2019).

Os osteoclastos são células grandes, multinucleadas, que são originadas de células progenitoras hematopoéticas mononucleares da medula. Sua principal função é reabsorver o osso com a liberação de enzimas e ácidos que dissolvem e digerem a matriz mineralizada do osso. Devido à sua função, os osteoclastos estão envolvidos no reparo ósseo após alguma lesão (ANSARI, 2019).

O processo de formação óssea foi inicialmente descrito por Frost e colaboradores em 1965 e acredita-se que pode ser influenciada por fatores genéticos em combinação com fatores ambientais como esforço físico, e, provavelmente, por fatores hormonais também (LANGDAHL; FERRARI; DEMPSTER, 2016). Este processo pode ocorrer por duas vias: ossificação endocondral e ossificação intramembranosa. Normalmente a ossificação endocondral ocorre nos membros e parte do esqueleto axial que suporta o peso, incluindo ossos longos e curtos, e a intramembranossa principalmente nos ossos chatos/planos do crânio e face, além de participar da ossificação de ossos curtos e do crescimento em espessura dos ossos longos, conforme FIGURA 2.

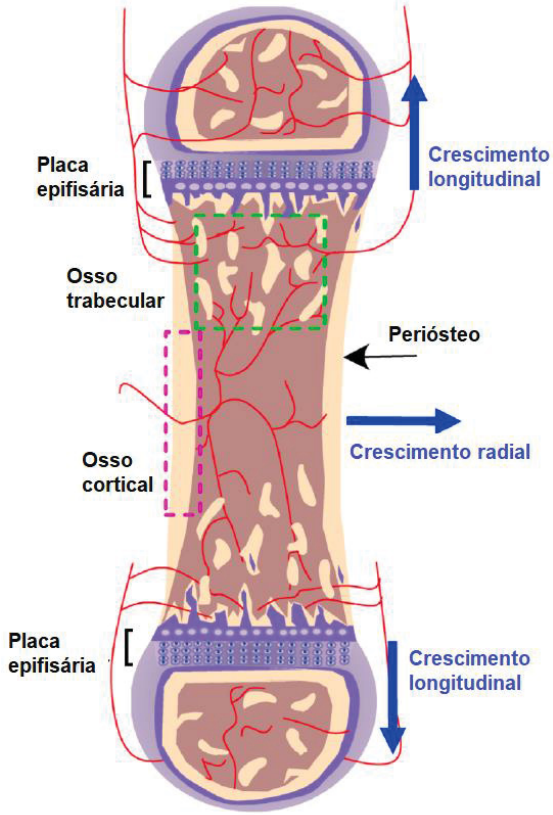
FIGURA 2 – OSSOS FORMADOS POR OSSIFICAÇÃO ENDOCONDRAL E OSSIFICAÇÃO INTRAMEMBRANOSA



FONTE: (CHAN et al., 2021)

Na ossificação endocondral (FIGURA 3), as células progenitoras mesenquimais se diferenciam em condrócitos que formam um molde de cartilagem hialina no formato do futuro osso. Os condrócitos sofrem hiperplasia e hipertrofia e a matriz circunvizinha é reduzida e mineralizada. A maior parte da cartilagem calcificada sofre degradação e é parcialmente removida; certa quantidade, no entanto, permanece na forma de espículas irregulares. Ocorre invasão de capilares e células osteoprogenitoras e desenvolve-se o tecido medular e ósseo sobre a estrutura das espículas. Essas espículas persistem por um curto período até que o componente cartilaginoso calcificado seja removido, permanecendo numa região conhecida como placa epifisária. O crescimento longitudinal do osso endocondral depende da atividade da placa epifisária e ao fim do crescimento a cartilagem vai se tornando mineralizada até ser totalmente substituída por tecido ósseo. Nas bordas periféricas do osso é formado o osso denso, mantido posteriormente pelo processo de remodelação óssea. Também ocorre o crescimento radial a partir da superfície óssea externa, o periósteo (SIMS, 2021).

FIGURA 3 – DIAGRAMA DE UM OSSO LONGO EM CRESCIMENTO



FONTE: (SIMS, 2021)

Já na ossificação intramembranosa, que acontece na mandíbula e maxila (SALHOTRA et al., 2020), ocorre migração de células mesenquimais derivadas de linhagens embrionárias para o local onde será formado o novo osso. Em seguida, essas células se multiplicam e se diferenciam em osteoblastos que formarão diretamente o novo osso (BERENDSEN; OLSEN, 2015).

2.1.2 Remodelação óssea

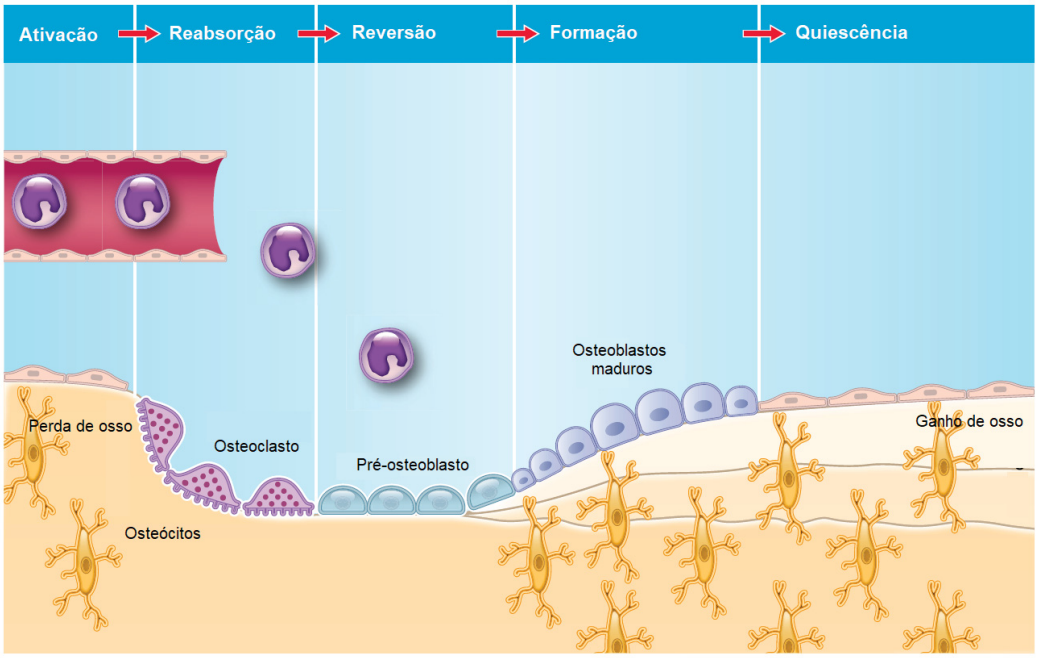
Após a formação dos ossos, o esqueleto adulto é totalmente renovado a cada 10 anos graças ao processo de remodelação óssea (LANGDAHL; FERRARI; DEMPSTER, 2016). Algumas células, como os osteoblastos e osteoclastos estão envolvidas nesse processo e ficam organizadas em unidades conhecidas como unidades ósseas multicelulares (BMU) (LANGDAHL; FERRARI; DEMPSTER, 2016).

A remodelação óssea nada mais é do que a reabsorção do tecido ósseo presente no esqueleto e a formação de novo tecido ósseo. Esse processo inicia-se na vida fetal e continua durante toda a vida e tem como objetivo adaptar a forma óssea para as demandas mecânicas ao longo da vida, desde o crescimento até o envelhecimento (BOLAMPERTI; VILLA; RUBINACCI, 2022).

Essa remodelação pode ser ativada por fatores locais, como forças mecânicas, ou sistêmicos, como hormônio da paratireoide (PTH), 1,25-dihidroxe vitamina D, calcitonina, glicocorticoides, hormônios da tireoide, hormônios gonadotróficos e citocinas. Por ser um processo natural, geralmente, a taxa de reabsorção é semelhante a taxa de deposição de novo osso. Uma das consequências do desbalanço desse processo é a osteoporose (LUPSA; INSOGNA, 2015).

O processo de remodelação óssea é dividido em quatro principais fases, que apesar de se sobreporem, podem ser tradicionalmente identificadas como: (I) fase de ativação, onde mediadores recrutam os osteoclastos progenitores para o local da remodelação; (II) fase de reabsorção, onde os osteoclastos amadurecem e reabsorvem o osso; (III) fase reversa, onde os osteoclastos morrem e os osteoblastos se multiplicam; (IV) e, por último, a fase de formação, onde nova matriz óssea é formada (osteóide) e posteriormente mineralizada (KIM, Jung-Min et al., 2020) (FIGURA 4). Adicionalmente, alguns autores pontuam a existência também das fases de quiescência e encerramento (SIDDIQUI; PARTRIDGE, 2016).

FIGURA 4 – PRINCIPAIS FASES DA REMODELAÇÃO ÓSSEA FISIOLÓGICA



FONTE: (SIDDIQUI; PARTRIDGE, 2016)

Dependendo da fase da remodelação, diferentes fatores estão envolvidos (TABELA 1). Os principais hormônios envolvidos na reabsorção são a calcitonina, hormônio da paratireoide, vitamina D3 e estrogênio. Além disso, fatores de crescimento têm sido associados, como reguladores do processo de remodelação, como por exemplo, IGFs, TGF-*β*, FGFs, EGF, WNTs e BMPs (SIDDIQUI; PARTRIDGE, 2016).

TABELA 1 – HORMÔNIOS E FATORES ENVOLVIDOS NO PROCESSO DE REMODELAÇÃO ÓSSEA EM CADA FASE

Fase da remodelação	**Hormônios e fatores que regulam a remodelação óssea**
Fase de ativação	+, PTH, IGF-1, IL-1, IL-6, PGE_2, Calcitriol, TNF-α. -, Estrogênio.
Recrutamento dos osteoclastos e fase de reabsorção	+, RANKL, M-CSF, αvβ3 integrinas, IL-1β, IL-1α, TNF-α, ácido retinóico, S1P. -, OPG, GM-CSF, estrogênio, Calcitonina, IL-4, IL-18, TGF-*β*.
Fase reversa	TGF-*β*, IGF-1, IGF-2, BMPs, PDGF, or FGF.
Recrutamentos dos osteoblastos e fase de formação	+, WNTs, BMPs, IGF-1, FGF-2, FGF-18, PDGFs, PTH, $1,25(OH)_2$ vitamin D_3, Runx2, TGF-*β*, CT-1, efrina B2. -, PDGFs, glicocorticoides, leptina, pirofostato, Sema4D.
Fase de encerramento	Sinal de feedback da expressão normal de esclerostina.

FONTE: (SIDDIQUI; PARTRIDGE, 2016)

2.2 OSSEOINTEGRAÇÃO

O conceito de osseointegração foi inicialmente observado e introduzido pelo ortopedista Per-Ingvar Brånemark (1924-2014) e colaboradores, em 1969. Em um estudo de microcirculação em coelhos, Brånemark descobriu que câmaras de titânio se incorporavam permanentemente no osso, não podendo ser retiradas sem que fossem fraturadas. Inicialmente, o termo foi estabelecido para a integração do titânio com o osso, mas, atualmente, é empregado para todos os materiais que se integram ao osso, inclusive cerâmicas (GUGLIELMOTTI; OLMEDO; CABRINI, 2019).

O processo de osseointegração se dá por três etapas: 1) após o trauma cirúrgico ocorre um processo inflamatório com liberação de mediadores químicos; 2) em seguida, há uma regeneração com a formação de tecido ósseo; 3) e, por fim, têm-se o período de maturação por mecanismos de remodelação óssea (COSTA JÚNIOR, 2011).

Entendendo mais profundamente o processo em si, a partir do momento que um implante é instalado, inicia-se um processo biológico, sendo as células sanguíneas (células vermelhas, plaquetas e células polimorfonucleares) as primeiras a chegarem no tecido que circunda o implante. Essas células são ativadas e começam então a produzir citocinas e fatores de crescimento e diferenciação. Todo esse processo leva à formação de coágulo, e a matriz de fibrina formada serve de arcabouço para migração (osteocondução), proliferação e diferenciação de células mesenquimais (osteoindução), principalmente de vênulas pós-capilares. Todo esse processo se dá 1 a 3 dias após a instalação do implante (LEE; BANCE, 2019; MAVROGENIS et al., 2009).

Nos primeiros 7 dias da instalação do implante, ocorre um extenso processo de angiogênese no espaço peri-implantar e, a partir do primeiro dia até 2 semanas, células mesenquimais se diferenciam em osteoblastos. Esses osteoblastos se aderem à superfície do implante, formando uma camada de matriz que, posteriormente, passará por um processo de maturação e formação do tecido ósseo maduro. Essa camada formada ainda possui baixa competência mecânica, mas por volta do décimo dia, começa a ser formado osso trabecular levando à fixação biológica ativa do implante com a diminuição do espaço entre a superfície do implante e o osso (LEE; BANCE, 2019; MAVROGENIS et al., 2009).

Após a osteogênese peri-implantar, ocorre o processo de remodelação óssea peri-implantar, que envolve a atuação dos osteoclastos e a substituição gradual do osso reticulado por osso lamelar.. Três meses após a instalação do implante, existe uma mistura de osso reticulado e lamelar, mas o estágio tardio da osseintegração pode levar um ano ou mais para ser atingido. Na área 1 mm ao redor da superfície do implante acontece remodelação constante devido ao estresse mecânico ao qual o implante é submetido (LEE; BANCE, 2019).

Quando o paciente não tem uma regeneração adequada, ocorre o reparo com a participação de citocinas que regem a formação de uma cicatriz composta por fibroblastos fusiformes, colágeno denso, fragmentos de tecido elástico e outros elementos da matriz extracelular. Além disso, essas citocinas também sinalizam para a produção de prostaglandinas e metaloproteases da matriz (SANTOS, Maria Cristina Leme Godoy dos, 2004). Quando esse processo ocorre, o paciente vivencia um episódio de falha de osseointegração.

Cortes histológicos podem comprovar a osseointegração pela visualização do contato do tecido ósseo com a superfície do implante. Clinicamente, alguns parâmetros podem ajudar na identificação da osseointegração, como: estabilidade do implante, através da mobilidade ou não deste; análise radiográfica, pela medição do nível ósseo; e, Análise de Frequência de Ressonância (RFA), que se utiliza da medição da vibração e análise estrutural (ATSUMI; PARK; WANG, 2007).

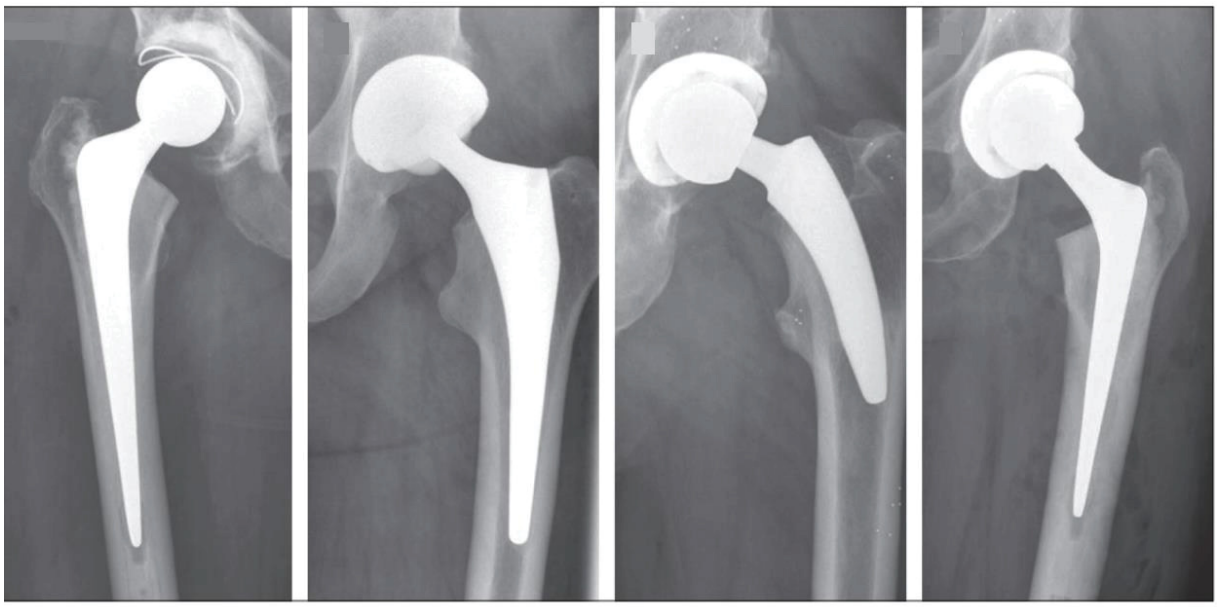
2.2.1 Implantes ortopédicos

Implantes ortopédicos são um conjunto de dispositivos médicos utilizados em cirurgias ortopédicas. Dentre os implantes ortopédicos, existem os parafusos, placas e próteses. Com relação às próteses, as mais comuns são as relacionadas às articulações. Os implantes de articulação, como por exemplo, quadril e joelho, são confiáveis e normalmente tem um ótimo custo-efetividade (CHENG et al., 2019).

A artroplastia total de quadril pode ser indicada em casos de osteoartrite (a grande maioria), fratura do pescoço femoral, necrose avascular, displasia e artrite inflamatória (FIGURA 5). A osteoartrite pode estar relacionada com fatores genéticos e ambientais. O tratamento com a prótese de quadril é indicado em casos de osteoartrite severa com dor nas articulações e resistentes a tratamentos sem intervenção cirúrgica. Ferramentas como *Oxford Hip Score e EuroQol five-domain*

Score são utilizadas para avaliar dor e situação funcional e qualidade de vida após o procedimento. A média de sobrevivência de um implante de quadril 14 anos após o procedimento é de 92,7% (FERGUSON et al., 2018).

FIGURA 5 – RADIOGRAFIA MOSTRANDO PRÓTESES TOTAIS DE QUADRIL



FONTE: (FERGUSON et al., 2018).

Pode haver necessidade de se realizar uma revisão, troca de um ou mais componentes da prótese, após o procedimento cirúrgico. O principal motivo para a realização de uma revisão é a perda asséptica, que ocorre devido ao desgaste que libera partículas no espaço articular levando à um processo inflamatório, e consequentemente à falha de ossointegração. Outro fator que pode levar à necessidade de revisão é o deslocamento (15%) que normalmente acomete o paciente no primeiro ano devido à fatores como idade, tônus musculares, ou movimentos específicos. Outros motivos comuns incluem infecção articular periprotética (9%), fratura periprotética (10%) e mal posicionamento do implante (5%) (FERGUSON et al., 2018).

2.2.2 Implantes dentários

Pacientes edêntulos ainda representam um desafio para a área odontológica. Muitas vezes, as limitações mastigatórias e fonéticas costumam causar alterações

estéticas que podem afetar a autoestima do paciente. Consequentemente, o tratamento desses pacientes tornou-se uma prioridade com demanda crescente, pois buscam melhorar sua qualidade de vida (MIGLIORANÇA et al., 2019).

Desde 1969, com a descoberta da osseointegração pelo ortopedista Dr. Per-Ingvar Brånemark (1929 – 2014) e associados, os pinos dentários (implantes) de titânio foram desenvolvidos e estão em constante processo de avanço tecnológico (BRÅNEMARK et al., 1977; CARLSSON et al., 1986). O tipo de material biocompatível, localização do implante, desenho do implante, técnicas cirúrgicas e protocolos de carregamento são os principais focos no processo de desenvolvimento da área de implantodontia (MIGLIORANÇA et al., 2019).

Atualmente, os implantes dentários são comumente usados para substituir dentes perdidos em uma variedade de condições clínicas e, portanto, diversos desenhos de implantes dentários estão disponíveis, entre eles os implantes convencionais unitários e os implantes zigomáticos.

Implantes de diferentes dimensões foram sendo fabricados ao longo do tempo para auxiliar no manejo de diferentes cenários clínicos no tratamento do edentulismo (AL-JOHANY et al., 2017). Os implantes convencionais são implantes indicados para pacientes que o cenário clínico não necessita de implantes especiais como implantes curtos, estreitos ou zigomático. Não existe um consenso muito claro na literatura sobre o comprimento de implante que é considerado convencional, mas de acordo com uma classificação proposta por AL-JOHANY et al.(2017), implantes maiores ou iguais a 10 mm e menores do que 13 mm são considerados convencionais.

Entre os implantes convencionais, também são encontradas diferentes geometrias, sendo as principais cilíndricas, cônicas e híbridas (corpo cilíndrico com geometria cônica na região do ápice) (FIGURA 6). As geometrias foram sendo modificadas ao longo dos tempos para que houvesse uma melhora na estabilidade primária e secundária dos implantes, aumentando a área de contato da superfície do implante com o osso que o circunda (WAECHTER et al., 2017).

FIGURA 6 – DESENHO ESQUEMÁTICO MOSTRANDO DIFERENTES MACRO-GEOMETRIAS DE IMPLANTES CONVENCIONAIS

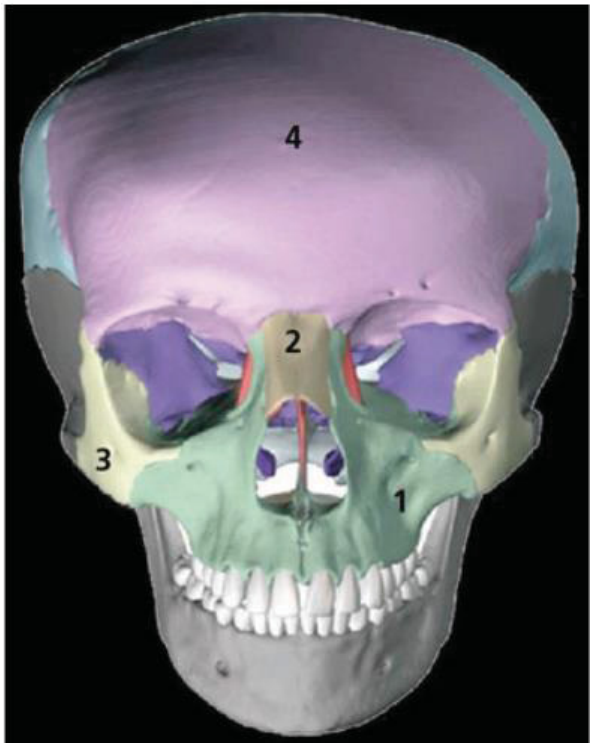
a) Implante cilíndrico; b) Implante cônico.
FONTE: (TORROELLA-SAURA et al., 2015)

2.2.2.1 Implante zigomático

Em 1998, Branemark publicou um estudo apresentando a técnica de instalação de implantes no osso zigomático. Os implantes zigomáticos têm sido utilizados para tratar pacientes edêntulos com atrofia alveolar severa da maxila (PETRUNGARO et al., 2018). Estes implantes são longos, em forma de parafuso, desenvolvidos como uma alternativa ao enxerto ósseo e são inseridos no corpo do osso zigomático (WU et al., 2019). Suas principais vantagens são que a enxertia óssea pode não ser necessária e os pacientes são reabilitados com próteses fixas muito mais precocemente, reduzindo o número de procedimentos cirúrgicos. Como esses pacientes geralmente são idosos, essa alternativa se torna ainda mais importante (ESPOSITO; WORTHINGTON, 2013; ROSENSTEIN; DYM, 2021).

Anatomicamente, o osso zigomático tem forma piramidal e contém osso cortical e trabecular denso (FIGURA 7) (ATT; BERNHART; STRUB, 2009). Os implantes zigomáticos são geralmente inseridos através da crista alveolar do seio maxilar para envolver o corpo ósseo zigomático (osso facial). Dependendo da anatomia local, para favorecer a saída do implante em uma posição menos palatina e para minimizar os riscos de complicações, como sinusites, os implantes zigomáticos também são colocados lateralmente ao seio, sem abertura da cavidade sinusal (APARICIO et al., 2014; ESPOSITO; WORTHINGTON, 2013; SHARMA; RAHUL, 2013).

FIGURA 7 – REPRESENTAÇÃO DO ESQUELETO FACIAL.



Legenda: (1) osso maxilar, (2) ossos nasais, (3) osso zigomático e (4) osso frontal.
FONTE: (GAUDY et al., 2014)

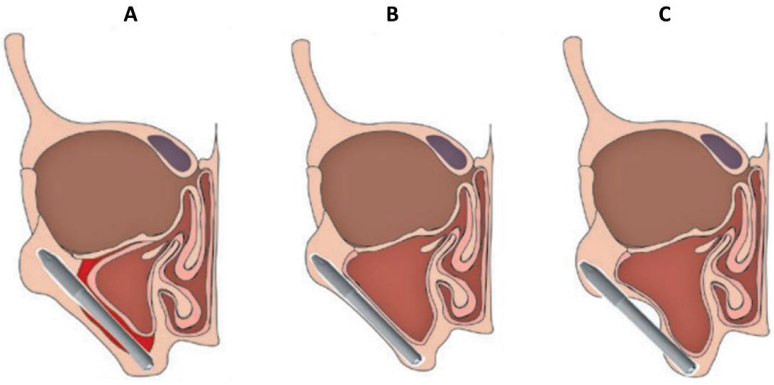
A preferência por uma técnica depende da escolha do cirurgião, da anatomia da crista alveolar, do seio maxilar, da concavidade da parede lateral do seio maxilar e do osso zigomático (YALÇIN et al., 2020). A técnica original proposta por Brånemark preconiza o uso de dois implantes zigomáticos intrasinusais, juntamente com dois ou quatro implantes convencionais na pré-maxila. Após realizar uma janela óssea na região mais superior e lateral da parede anterior do seio maxilar e levantar a membrana sinusal, o implante zigomático é colocado na crista do rebordo alveolar, passando próximo ao pilar zigomático, sendo guiado pela cavidade do seio maxilar. A posição do implante é palatinizada na região do segundo pré-molar (FIGURA 8A) (ARAÚJO et al., 2016). Nesse protocolo existe a necessidade de preservar e elevar a membrana sinusal. A posição da plataforma do implante na abordagem extremamente palatalizada pode causar desconforto ao paciente na maioria dos casos. Outro fator a ser considerado nessa técnica é a biomecânica de todo o conjunto protético de reconstrução, que pode ser sobrecarregado devido à criação de um cantilever vestibular. Além disso, como o implante está localizado dentro do seio maxilar a partir da borda remanescente, há mais suscetibilidade a

comunicações bucais sinusais e sinusite (APARICIO et al., 2021; DE CARVALHO et al., 2022).

Em 2000, Stella e Warner apresentaram uma técnica simplificada do protocolo original com o uso de uma abordagem "*sinus slot*" ou "*in-the-wall*" (FIGURA 8B). Essa técnica baseia-se em marcações na parede anterior do seio maxilar, por onde é guiada a instalação do implante zigomático, eliminando a janela óssea, e levantando a membrana do seio maxilar, proporcionando maior interface osso-implante, com orientação mais vertical da fixação. Eles também relataram que o aspecto mais importante é o posicionamento da plataforma do implante próximo à crista do rebordo alveolar (STELLA; WARNER, 2000). Esta técnica traz melhorias significativas em comparação com o protocolo original publicado.

Outra técnica de instalação é a extrasinus (*in-out-in*), onde o implante fica totalmente fora do seio maxilar. No entanto, uma porção do implante pode ser ancorada no osso alveolar da crista maxilar, se este estiver presente (FIGURA 8C) (ARAÚJO et al., 2016; BLANC et al., 2020). Neste método o implante é instalado numa abordagem exteriorizada ao seio maxilar, otimizando a posição protética, coincidindo com o rebordo ósseo. Consequentemente, o risco de contaminação do seio maxilar através do sulco peri-implantar e o risco de sinusite são menores. Uma vantagem desse protocolo é que não necessariamente é feito um *slot* na parede lateral do seio, pois o implante é apoiado dentro, ou parcialmente no rebordo, o que determina a posição do implante na posição protética ideal de acordo com a anatomia do paciente (DE CARVALHO et al., 2022).

FIGURA 8 – TÉCNICAS PARA INSTALAÇÃO DE IMPLANTES ZIGOMÁTICOS



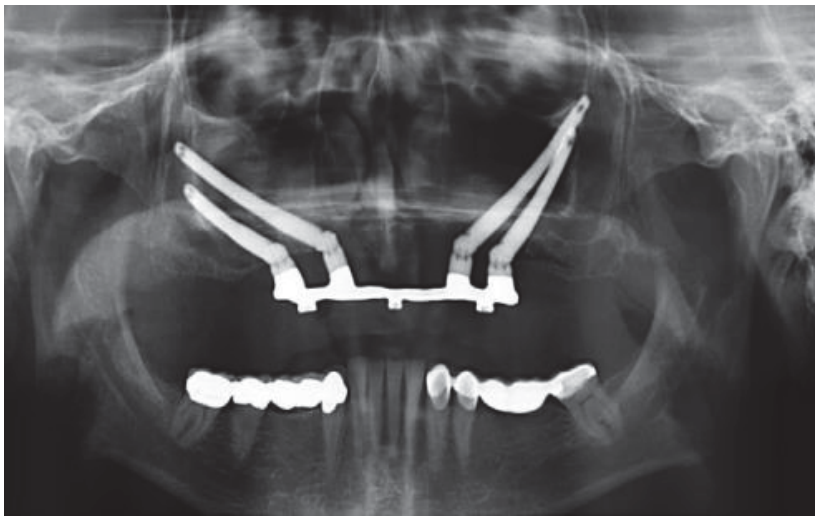
(A) Técnica original de Brånemark (intrasinus). (B) Técnica de *slot sinus*. (C) Técnica extra-sinusal.

FONTE: (ARAÚJO et al., 2016; YALÇIN et al., 2020)

O tratamento da maxila atrófica pode ser realizado com um implante zigomático colocado em cada lado da maxila posterior combinado com dois ou mais implantes convencionais colocados na maxila anterior (DAVÓ; DAVID, 2019; ROSENSTEIN; DYM, 2021). Para pacientes sem osso maxilar anterior suficiente, 2 ou mais implantes zigomáticos devem ser colocados em cada lado da maxila posterior (PETRUNGARO et al., 2018; ROSENSTEIN; DYM, 2021). Existe também o conceito de *quad* zigoma, que é o uso de 4 implantes zigomáticos para reabilitação protética (FIGURA 9) (DAVÓ; DAVID, 2019; PETRUNGARO et al., 2018).

Diversos comprimentos de implantes zigomáticos são encontrados na literatura, variando de 30 a 62,5 mm, com diâmetro apical de 3,75 mm a 4 mm e diâmetro crestal de 4 mm a 5 mm, sendo esses comprimentos e diâmetros dependentes da marca do implante (CANDEL-MARTÍ et al., 2012; CHRCANOVIC; ABREU, 2013; HOEFLER; AL-SABBAGH, 2019; PETRUNGARO et al., 2018; SHARMA; RAHUL, 2013). Sharma e Rahul (2013) relataram que o comprimento e a posição dos implantes zigomáticos são determinados pela anatomia do processo zigomático e das estruturas adjacentes e que o tamanho do defeito, osso residual e cobertura de tecido mole são fatores que ajudam a determinar o comprimento e a angulação de instalação do implante (SHARMA; RAHUL, 2013). Para compensar a angulação entre o zigoma e a maxila, componentes angulados (ângulo de 45° ou 55°) ou implantes angulados podem ser utilizados (ATT; BERNHART; STRUB, 2009; CHRCANOVIC; ABREU, 2013).

FIGURA 9 – IMPLANTES ZIGOMÁTICOS INSTALADOS PELO CONCEITO DE QUAD ZIGOMA



FONTE: (DAVÓ; DAVID, 2019).

O tratamento de maxilas edêntulas com os implantes zigomáticos requer amplo conhecimento da anatomia e fisiologia da região maxilofacial. O treinamento adequado, incluindo a compreensão dos princípios biomecânicos protéticos e cirúrgicos, é essencial para uma reabilitação dentária bem-sucedida. É um procedimento arriscado, uma vez que estruturas anatômicas delicadas, como órbita e cérebro podem estar envolvidas (BEDROSSIAN; BEDROSSIAN, 2018; PETRUNGARO et al., 2018; WU et al., 2019). A principal complicação que parece ocorrer com os implantes zigomáticos é a sinusite, que pode se desenvolver vários anos após a instalação da prótese e tratada com uso de antibióticos e resolvida sem complicações maiores (CANDEL-MARTÍ et al., 2012; CHRCANOVIC; ABREU, 2013; CHRCANOVIC; ALBREKTSSON; WENNERBERG, 2016; WANG et al., 2015),

Em uma extensa revisão da literatura, Bedrossian e Bedrossian (2018) descreveram problemas potenciais relacionados ao uso de implantes zigomáticos, entre eles: envolvimento orbital, envolvimento intracraniano, parestesia do nervo infraorbital, infecções subperiosteais, superextensão do ápice do implante zigomático, deiscência vestibular, implante fraturado e infecção sinusal (BEDROSSIAN; BEDROSSIAN, 2018). As taxas de complicações são relativamente baixas, raramente catastróficas e facilmente gerenciadas (TUMINELLI et al., 2017).

Existem algumas contraindicações para o uso de implantes zigomáticos, incluindo infecção aguda dos seios da face, patologia maxilar ou zigomática e pacientes incapazes de se submeter à cirurgia de implante devido à doença sistêmica não controlada ou maligna subjacente. As contraindicações relativas incluem sinusite infecciosa crônica, o uso de bifosfonatos e fumar mais de 20 cigarros por dia (APARICIO et al., 2014; ROSENSTEIN; DYM, 2021). Qualquer patologia do seio maxilar deve ser tratada antes da instalação do implante zigomático (APARICIO et al., 2014).

Não existem critérios específicos para avaliar o sucesso dos implantes zigomáticos, mas a maioria dos autores considera como critérios de avaliação, mobilidade, dor ou infecção nos implantes após carga protética e ausência de radioluscência peri-implantar. O sucesso médio ponderado para esses critérios após uma revisão de 15 estudos foi de 97,05% (CANDEL-MARTÍ et al., 2012).

2.2.2.2 Levantamento de seio

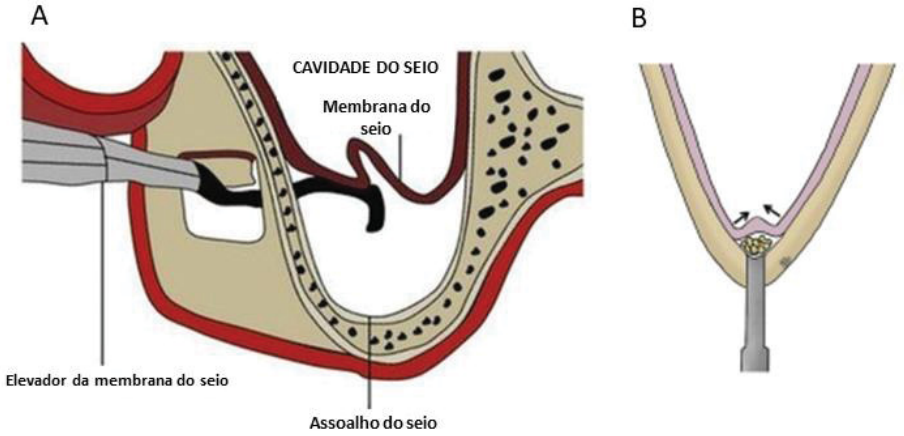
A reabilitação posterior da maxila com implantes dentários frequentemente enfrenta limitações quanto à disponibilidade óssea nesta região, bem como à alta prevalência de osso de baixa densidade. A perda óssea posterior é caracterizada por patologias dentais que afetam o osso alveolar, por técnicas de extração dentária traumática e por pneumatização do seio maxilar (ABUBAKER, 1999; CONRAD et al., 2011; LUNDBERG et al., 1995; ROSENFELD et al., 2015).

São aplicadas diferentes estratégias para superar os problemas que possam dificultar ou impossibilitar a instalação de implantes na maxila posterior. Uma dessas estratégias é a elevação do seio maxilar combinada ou não com enxerto ósseo. O procedimento de elevação do seio maxilar é um procedimento previsível e confiável para o tratamento destes pacientes (MAESTRE-FERRÍN et al., 2010; VELÁSQUEZ-PLATA et al., 2002). A realização de enxertos ósseos (autógenos, homógenos, heterógenos e aloplástico) para devolver a altura óssea no seio maxilar para instalação de implantes dentários também já é bem estabelecida na prática clínica.

Algumas abordagens podem ser seguidas para a realização do levantamento de seio, sendo as duas principais as da janela lateral e a transcrestal. A abordagem da janela lateral foi desenvolvida por Cadwell-Luc e modificada por Tatum em 1986 (TATUM, 1986). A técnica consiste em realizar a abertura de uma janela óssea na parede medial do seio maxilar com instrumentos rotatórios ou pizoelétricos com posterior elevação da membrana do seio e colocação do material de enxerto. Por essa abordagem é possível ganhar mais de 10 mm de espaço para colocação de enxerto ósseo (FIGURA 10A) (CORREIA et al., 2012).

Já a abordagem transcrestal (FIGURA 10B) é considerada minimamente invasiva e foi introduzida em 1977 por Tatum, e modificada posteriormente por Summers em 1994 (SUMMERS, 1994). A técnica consiste basicamente em dois passos: 1) criação de um acesso à membrana pelo local de instalação do implante; 2) a membrana do seio maxilar é deslocada para criação do espaço necessário. O deslocamento da membrana pode ser realizado por diferentes maneiras utilizando osteótomo, instrumentos rotatórios, combinação de osteótomo e broca trefina e dispositivos infláveis. Por essa abordagem é possível ganhar entre 3 a 4 mm de espaço para colocação de enxerto ósseo (FARINA et al., 2022).

FIGURA 10 – DESENHO ESQUEMÁTICO DEMONSTRANDO AS TÉCNICAS DE ELEVAÇÃO DE SEIO MAXILAR



(A) Técnica de levantamento do seio maxilar pela abordagem da janela lateral; (B) Técnica de levantamento do seio maxilar pela abordagem transcrestal.

FONTE: (MAVINKURVE; BHANGE, 2020; STACCHI et al., 2022)

Os implantes intrasinus têm uma alta taxa de sobrevivência (FUGAZZOTTO; VLASSIS, 1998) e sua instalação pode ser realizada em um procedimento de uma fase ou duas fases. O procedimento de uma fase, onde a elevação do seio maxilar é realizada simultaneamente à instalação do implante, geralmente é realizado quando se tem altura óssea residual de pelo menos 5 mm. Já o procedimento de duas fases é indicado em altura óssea residual entre 1 e 4 mm e é necessário esperar alguns meses após o enxerto para a instalação dos implantes (CORREIA et al., 2012).

As contraindicações do levantamento de seio são as mesmas da instalação de qualquer implante, exceto que a presença de patologias nos seios, incluindo sinusite aguda, pólipos, cistos e tumores, podem comprometer o procedimento. Adicionalmente, o uso de esteroides inaláveis e dependência em cocaína também são contraindicações para a utilização desta técnica (KAUFMAN, 2003).

Apesar do levantamento de seio ser uma técnica bastante difundida e com resultados positivos comprovados, algumas complicações trans e pós-operatórias são bastante comuns. Complicações como perfuração da membrana sinusal, sinusite, sangramento devido a danos em veias, infecção da ferida, perda parcial ou total do enxerto ósseo, deiscência do tecido mole ou duro, dor de cabeça, edema temporário, desconforto e hematomas são complicações comuns após o procedimento de levantamento de seio. A maioria das complicações após o

procedimento são transitórias e podem ser resolvidas com o uso de analgésico e antibióticos sistêmicos (HSU et al., 2022).

2.2.2.3 Sinusite

Entre as complicações da instalação dos implantes zigomáticos e também dos procedimentos de levantamento de seio desponta significativamente a sinusite.

Sinusite, mais corretamente chamada de rinossinusite, é uma inflamação dos seios paranasais que afeta as membranas e mucosas que revestem o nariz e os seios faciais (ABUBAKER, 1999). A presença da sinusite pode atrapalhar a correta drenagem de secreção dos seios da face (ADAMS et al., 2008) e com isso causar dor na região da face, corrimento e congestão nasal, tosse, febre e mau hálito (ANDERSON; AARONSON; WILKIN, 1993).

A sinusite pode ser aguda ou crônica. A sinusite aguda é definida como a sinusite que persiste por até 4 semanas e tipicamente é devido à uma infecção do trato respiratório superior, geralmente causada por vírus, apesar de também poder ser causada por bactérias. Já a sinusite crônica é caracterizada pela persistência dos sintomas por pelo menos 12 semanas (SOHAL; TESSEMA; BROWN, 2016).

O tratamento das sinusites pode ser feito de várias maneiras, dependendo se é sinusite aguda ou crônica. Caso a sinusite seja causada por bactéria, a antibioticoterapia é uma opção de tratamento, tendo a amoxicilina como opção de primeira linha. Além disso, também podem ser utilizadas terapias adjuvantes com a utilização de descongestionantes, mucolíticos, solução salina nasal, corticosteroides e expectorante (ROSENFELD et al., 2015; SOHAL; TESSEMA; BROWN, 2016).

2.2.3 Complicações dos implantes osseointegráveis e polimorfismos genéticos

Como todo e qualquer procedimento cirúrgico, a instalação de implantes ortopédicos ou dentários pode levar a complicações. Apesar de procedimentos bem-sucedidos, avanços na área de biomateriais e aperfeiçoamento nos tratamentos de superfície dos implantes terem levado a maioria dos procedimentos a alcançarem a osseointegração com sucesso, falhas ainda ocorrem. Essas falhas podem ser divididas em 4 grupos: falhas biológicas (ex. dificuldade no processo inicial de cicatrização do osso), mecânicas (ex. fraturas de implantes), iatrogênicas (ex.

remoção de implantes devido à violação das estruturas anatômicas vizinhas) e adaptação inadequada (ex. insatisfação estética por parte do paciente e problemas psicológicos) (SAKKA; BAROUDI; NASSANI, 2012).

Falhas podem ser ainda classificadas como precoce, cujo comprometimento é mais associado a complicações cirúrgicas, volume e qualidade óssea inadequada, infecções pós-cirurgicas, inflamação excessiva, perda óssea marginal, contaminação bacteriana e osseointegração incompleta ou tardia, principalmente proveniente de processos patológicos atrelados ao estado de saúde geral do paciente e eventos sistêmicos de risco, como diabetes, artrite, obesidade, osteoporose, hábito tabagista, radioterapia, sobrecarga e periimplantite retrógrada entre outros (EKFELDT et al., 2001; ESPOSITO, M et al., 1998; PAQUETTE; BRODALA; WILLIAMS, 2006).

Mesmo com todos os cuidados clínicos e exames prévios, existem alguns pacientes que desenvolvem repetidas perdas do implante sem causas clinicamente reconhecidas, sugerindo uma incapacidade na remodelação (DEAS et al., 2002; YESHWANTE et al., 2015). Dessa maneira, parece existir um grupo de risco, indicando que fatores intrínsecos ao indivíduo, inclusive fatores genéticos, desempenham papel importante na sobrevivência dos implantes osseointegrados e que podem estar influenciando a resposta durante a osseointegração.

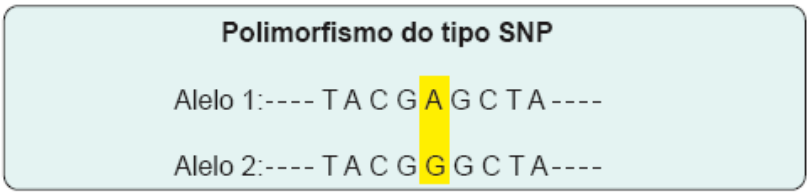
Avanços significativos nos estudos relacionados a susceptibilidade genética para o fenótipo clínico de perda do implante têm sido baseados na análise de genes candidatos com o objetivo de encontrar marcadores genéticos para osseointegração, os polimorfismos.

O conceito de polimorfismo pode variar dependendo da área que o estuda. Quando se fala de genética de populações, entende-se polimorfismo como uma alteração genética onde o alelo mais comum tem uma frequência maior do que 1% na população. Já no cenário clínico, na genética médica, polimorfismo se refere a qualquer gene ou alelo que possui mais de uma forma, não importando aqui a frequência. Nesse caso, olha-se para o indivíduo e não para a população (SCHAEFER; THOMPSON, 2015).

Dentre os tipos de polimorfismos, existe o polimorfismo de nucleotídeo único (SNP – *Single Nucleotide Polymorphism*). Os SNPs envolvem a troca de pares de nucleotídeos únicos, por exemplo, substituição de G:C por A:T (FIGURA 11). Normalmente esses SNPs ocorrem em regiões não codificadoras e dificilmente levam ao desenvolvimento de fenótipos mutantes (SNUSTAD; SIMMONS, 2008).

Estima-se que exista um SNP a cada 1000 pares de bases no genoma humano, o que significa que uma pessoa pode ter mais de 3 milhões de SNPs (SCHAEFER; THOMPSON, 2015).

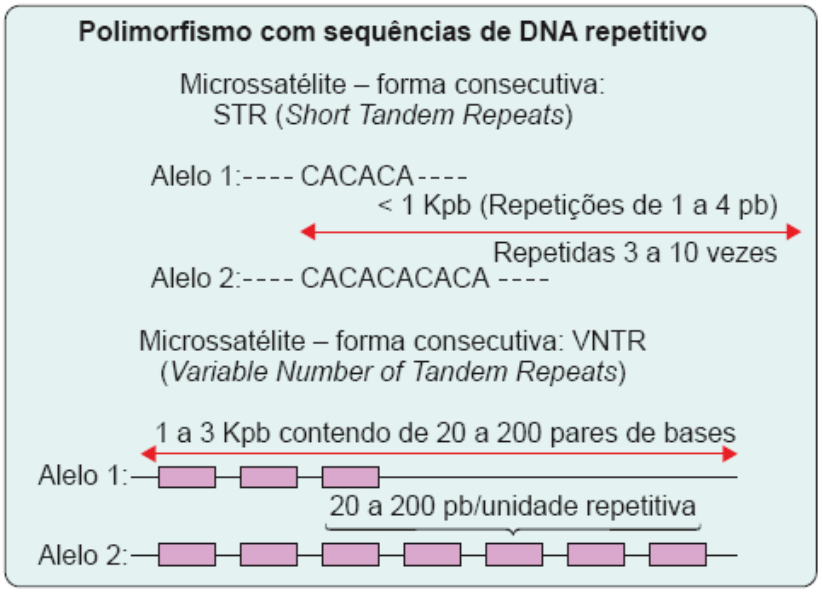
FIGURA 11 – REPRESENTAÇÃO ESQUEMÁTICA DA SUBSTITUIÇÃO DE UM NUCLEOTÍDEO (SNP)



FONTE: (MENCK; SLUYS, 2017)

Existem também os polimorfismos com sequência de DNA repetitivo de maneira consecutiva. Dentre esses polimorfismos está, por exemplo, os microssatélites que são repetições de 1 a 4 pares de bases (*Short Tandem Repeats* - STR) em um determinado locus que pode se estender em até 1 Kpb. Também existem as repetições de maneira mais dispersa chamadas de *Variable Number of Tandem Repeats* – VNTR (FIGURA 12) (MENCK; SLUYS, 2017).

FIGURA 12 - REPRESENTAÇÃO ESQUEMÁTICA DE POLIMORFISMO COM SEQUÊNCIA DE DNA REPETITIVO



FONTE: (MENCK; SLUYS, 2017).

Na literatura, correlação entre SNPs e diferentes patologias já foram identificadas inclusive em desordem musculoesqueléticas e patologias orais. Peri-implantite, uma inflamação progressiva do tecido mole ao redor do implante, foi recentemente associada, através de uma metanálise, ao polimorfismo rs2073618 no gene da proteína osteoprotegerina, uma proteína envolvida no processo de reabsorção óssea. Ambos os genótipos recessivos e homozigotos foram relacionados ao risco aumentado de desenvolver peri-implantite, podendo se tornar um potencial biomarcador (XU et al., 2022). Adicionalmente, o polimorfismo rs4072111 no gene da Interleucina-16, já foi correlacionado com maior suscetibilidade de desenvolver peri-implantite na população chinesa (CHEN, Zongfei; CHEN, 2021).

É importante pontuar que nem sempre os polimorfismos estão correlacionados negativamente com uma doença, podendo, em alguns casos, conferirem proteção à determinada condição. O estudo de Zhao e Li (2018) demonstrou que o polimorfismo rs1800795, também conhecido como -174 G/C, no gene da interleucina-6 confere proteção ao desenvolvimento de periodontite moderada e severa na população brasileira.

Deng et al. (2022), por meio de uma metanálise, analisaram a associação de polimorfismos no gene da interleucina-6 com o risco de desenvolver osteoartrite. A osteoartrite é uma doença debilitante que atinge primeiramente os joelhos, quadril e coluna e tem uma série de característica, como por exemplo, degradação da cartilagem articular. A interleucina-6 é uma citocina pró-inflamatória excretada por diversas células, inclusive no microambiente das articulações e já foi associada com outras doenças muscoloesqueléticas como, por exemplo, osteoporose e degeneração do disco intervertebral (FISCHER; HAFFNER-LUNTZER, 2022; RISBUD; SHAPIRO, 2014). Na metanálise em questão, os polimorfismos rs1800796 no gene da interleucina-6 foi associado a um risco maior de desenvolver osteoartrite.

Ainda relacionado a desordens muscoesqueléticas, o polimorfismo rs12722 no gene colágeno tipo V α1 está associado a uma suscetibilidade maior a danos ao ligamento, especialmente na população caucasiana. Já os polimorfismos rs13946, rs71746744 e rs3196378 parecem ter tendência de conferir um risco elevado de danos nos tecidos moles muscoesqueléticos (GUO et al., 2022).

2.3 METALOPROTEASE

Entre as inúmeras moléculas importantes envolvidas no processo de osseointegração, as metaloproteases da matriz (MMPs) merecem especial atenção, já que estão envolvidas desde a remodelação óssea até processos inflamatórios.

As MMPs são uma família de endoprotease dependente de zinco que desempenham papel vital na proteólise de componentes estruturais e de sinalização da matriz extracelular, sendo que sua atividade influencia a diferenciação, migração, invasão e proliferação celular (CAUWE; VAN DEN STEEN; OPDENAKKER, 2007; ITOH; SEIKI, 2006; PAIVA; GRANJEIRO, 2014). Ainda estão envolvidas na cicatrização de feridas (WOESSNER, 1991), na angiogênese (NEWBY, 2005), na reposição celular, remielinização e restabelecimento de conectividade e integridade neurovascular e remodelação óssea (HUNTLEY, 2012).

Estas proteases são secretadas por diversos tipos celulares e muitas de suas atividades biológicas são exercidas em ambiente extracelular, onde influenciam criticamente o comportamento celular, atuando sobre substratos variados. As MMPs tem a capacidade de degradar praticamente toda a matriz extracelular, membrana basal e seus componentes como colágenos, fibronectina, laminina, vitronectina e outras (BIRKEDAL-HANSEN, 1993; CAUWE; VAN DEN STEEN; OPDENAKKER, 2007); além de influenciar peptídeos de fator de crescimento, citocinas, moléculas de adesão celular e muitos outros tipos de receptores e glicoproteínas residentes na superfície celular (BUTLER; OVERALL, 2009; STERNLICHT; WERB, 2001).

A família das metaloproteases de matriz é constituída de 28 membros com pelo menos 23 sendo expressas em humanos e são classificadas da seguinte forma: colagenases, gelatinases, estromelisinas, matrilisinas e metaloproteases do tipo membrana (MT-MMPs) (TABELA 2) (CUI; HU; KHALIL, 2017).

TABELA 2 – CLASSIFICAÇÃO DAS METALOPROTEASES DE ACORDO COM A SUA CLASSIFICAÇÃO POR TIPO E DESCRIÇÃO DE SUBSTRATOS.

Tipo	Substratos	**MMPs**
Colagenases (1–4)	colágeno II, II, III, VIII, X, gelatina, agrecan, entactina	MMP-1, -8,-13, -18
Gelatinases (A e B)	gelatina, colágenos I, IV, V, VII, X, XI, fibronectina, elastina, laminina, vitronectina, proMMPs-9 e 13	MMP-2, MMP-9
Estromelisinas	proteoglicanos, laminina, gelatina, fibronectina, entactina, colágenos III, IV, V, IX, X, XI, proMMPs 1, 8, 9 e 13, vitronectina, inibidor α 1-proteinase	MMP-3, -10, -11
Matrilisinas	proteoglicanos, laminina, fibronectina, gelatina, entactina, colágeno IV, elastina, tenascina	MMP-7, MMP-26
Metaloproteases do tipo membrana	colágeno I, II, III, gelatina, fibronectina, laminina, proteoglicanos, proMMP-2 e13	MMP-14,-15, -16, -17, -24, -25

FONTE: (CABRAL-PACHECO et al., 2020).

As MMPs são amplamente distribuídas, com suas estruturas bastante conservadas (MCGEEHAN et al., 1992). Todas elas possuem uma sequência gênica com alta taxa de similaridade, sugerindo que foram duplicadas a partir de um gene ancestral comum. Dos genes das MMPs humanas, oito estão no cromossomo 11 (SHAPIRO, 1998). Outros genes que as sintetizam estão distribuídos entre os cromossomos 1, 8, 12, 14, 16, 20 e 22 (SHAPIRO, 1998).

A maioria das MMPs são sintetizadas e secretadas na forma inativa (zimógenos); são convertidas para atividade proteolítica por meio de vários processos regulatórios (HUNTLEY, 2012), que ocorrem a nível transcricional, traducional e pós traducional (STERNLICHT; WERB, 2001). A ativação enzimática requer a remoção do domínio pró-peptídeo por meio da degradação por proteases e sua atividade pode ainda ser regulada por citocinas, hormônios, fatores de crescimento, estresse de cisalhamento ou oxidativo (SPINALE, 2007).

Várias metaloproteinases possuem uma sequência sinal N-terminal que são reconhecidas por receptores de membrana translocadores responsáveis por secretar proteínas, como MMP-1 e MMP-8; enquanto outras não possuem essa sequência, ficando associadas à membrana, como a MMP-14 (CABRAL-PACHECO et al.,

2020). Em condições fisiológicas normais, as MMPs podem ser reguladas de quatro formas: na transcrição, ativação de precursores de zimogênio, interação com componentes específicos da matriz extracelular e diretamente por uma proteína inibidora (CABRAL-PACHECO et al., 2020). Esse inibidores proteolíticos podem ser a α2-macroglobulina (proteína plasmática que age como um inibidor de proteases) ou seus inibidores teciduais específicos (TIMPs) (LENGLET; MONTECUCCO; MACH, 2015).

De modo geral, a regulação das MMPs é extremamente precisa porém, em alguns casos, modificações que ocorrem em certos nucleotídeos podem influenciar a regulação transcricional, consequentemente, alterar a quantidade de MMPs secretada pela célula local (CARGILL et al., 1999).

Nesse trabalho, após a realização da revisão sistemática, foi foco de estudo os polimorfismos nos genes que codificam as colagenases 1 e 8 (MMP1 e MMP8) e estromelisina 3 (MMP3)..

A MMP-1, também conhecida como colagenase-1, é uma importante proteinase da família MMP que degrada principalmente o colágeno tipo I, a proteína mais abundante no corpo. Ela altera o microambiente no seu entorno, o que pode estar relacionado com a invasão de metástase e desenvolvimento de diferentes cânceres (LI et al. 2018). A literatura já demostrou seu envolvimento em patologias orais e musculoesqueléticas e alguns polimorfismos genéticos nas MMP-1 já foram identificados como fator de risco. Entre eles o SNP MMP-1 g.-1607 G>GG (rs1799750), localizado na região promotora do gene da MMP-1, que já foi correlacionado com risco aumentado de osteoartrite na população chinesa (GENG et al., 2018) e em populações jovens com menos de 60 anos de idade (XU, Bo et al., 2019). Adicionalmente, este mesmo polimorfismo pode ser utilizado como biomarcador para uma maior suscetibilidade à ruptura do manguito rotador (MIAO et al., 2019). Por fim, o SNP rs1799750 também é um fator de risco para a perda precoce de implante dentário (DE ARAUJO MUNHOZ et al., 2018).

Apesar de não haver estudos mais recentes com o SNP rs1144393, este polimorfismo, caracterizado pela substituição de uma base adenina por guanina, já foi associado com tendinopatia tibial posterior, contribuindo para o aumento do risco de desenvolver essa disfunção (BARONEZA et al., 2014) ecom o desenvolvimento de osteomielite e perda de implante dentário (DE ARAUJO MUNHOZ et al., 2018; KONG et al., 2017). Já os estudos com o polimorfismo rs5854 são raros na literatura,

sendo que nenhum deles é recente. Mas associação deste polimorfismo com falha precoce em artroplastia total de quadril e câncer de células escamosas orais já foram relatadas (ERDEI et al., 2013; YAN et al., 2014).

Já a MMP-3 atua tanto na degradação da matriz extracelular como fator de transcrição no núcleo, participando na ativação de outras MMPs, como as MMP-1, MMP-7 e MMP-9 (MITTAL et al., 2016). Por atuar na degradação de cartilagem, pode estar envolvida na patogênese e progressão de osteocondropatias, como a doença de Kashin-Beck (SHI et al., 2022). Os níveis de MMP-3 no líquido sinovial pode ser utilizada como biomarcador para artrite psoriática (GENEVA-POPOVA et al., 2022). A região promotora dogene da MMP-3 apresenta o SNP MMP-3 g. -1612 5A>6A (rs3025058) associado a modificações nos níveis expresso das MMP-3. Esse SNP já foi relacionado a periodontite inicial (HEIKKINEN et al., 2016), ao aumento do risco de câncer bucal (NOSRATZEHI; ALIJANI; MOODI, 2017), aumento do risco de danos aos ligamentos e tendões, especialmente em população caucasiana e brasileira (GUO; AIZEZI; et al., 2022) e doença da artéria coronária em pacientes maiores do que 50 anos de idade (GHAFFARZADEH et al., 2019).

A MMP-8 desempenha papel especial na inflamação e em processos destrutivos ao redor de implantes, tendo em vista que os substratos de preferência dessas enzimas são os colágenos tipos I, II, III e IV, importantes proteínas do tecido ósseo, bem como dos tecidos moles ao redor dos implantes (BIRKEDAL-HANSEN, 1993). Estudos indicaram que os níveis de MMP-8 são significativamente maiores no fluido gengival crevicular (KONOPKA; PIETRZAK; BRZEZIŃSKA-BŁASZCZYK, 2012). Aleksandrowicz et al. (2017) sugerem que o monitoramento do nível de MMP-8 no fluido sulcular periimplantar (PISF) poderia ajudar a diagnosticar a mucosite e/ou periimplantite em estágio inicial, antes das manifestações clínicas, fato que permitiria o início rápido da terapia apropriada. Além disso, a MMP-8 é citada como uma forte candidata a biomarcador para detectar destruição óssea alveolar em periodontite (GURSOY et al., 2013) e perda óssea progressiva na periimplantite (ARAKAWA et al., 2012). O SNP MMP-8 g.-799 C>T (rs11225395) localizado na região promotora do gene da MMP-8 e responsável por alterações na expressão da proteína foi associado a diferentes cânceres como colorretal (TAI et al., 2020) e carcinoma de células escamosas da laringe (MORENO-ORTIZ et al., 2021). Também foi associado a espondilite anquilosante na população chinesa (MENG et al., 2018) e periodontite agressiva generalizada (LI et al., 2020).

Uma vez que as MMPs estão envolvidas em muitos e diversificados processos fisiológicos e patológicos, suas propriedades enzimáticas fazem delas um tópico de pesquisa essencial para compreender a osseointegração de implantes. O desafio atual da implantodontia parece estar na habilidade em detectar pacientes de risco e traçar estratégias de terapias individualizadas.

2.4 REVISÃO SISTEMÁTICA E METANÁLISE

Nos últimos anos, a revisão sistemática tem sido utilizada para avaliar progressos e inovações científicas. Esta metodologia é definida como uma sequência de estratégias metodológicas que auxilia na diminuição do viés por meio de uma busca sistemática, uma análise clínicia e criteriosa dos estudos e síntese de todos os estudos relevantes de um determinado tópico. A revisão sistemática utiliza uma metodologia com perguntas e métodos bem definidos para identificar, selecionar e avaliar estudos científicos (MANCHIKANTI et al., 2009).

Já a metanálise é uma técnica estatística usada para combinar dados individuais de diferentes pesquisas científicas sobre um tema, resultando em um único desfecho, aumentando o número amostral e a precisão desse desfecho. Isto, consequentemente, aumenta a confiabilidade e a qualidade técnica das revisões. Uma metanálise idealmente inicia com uma boa e não enviesada revisão sistemática e desde seu surgimento, esta técnica tem se tornado uma forma habitual de sintetizar evidências e resumir os resultados de estudos individuais e combinar vários resultados para validá-los (LABARCA; LETELIER, 2022).

Geralmente as revisões sistemáticas e metanálises são realizadas para analisar dados de estudos clínicos randomizados entretanto, muitas das perguntas da área da saúde são respondidas por meio de estudos observacionais e esse desenho de estudo representa a prática clínica diária. Portanto, atualmente, as revisões sistemáticas e metanálises podem ser realizadas com estudos observacionais. Um outro tipo de estudo que também pode ser utilizado é o estudo de acurácia diagnóstica (MANCHIKANTI et al., 2009).

A literatura relacionada aos implantes osseointegrados é abundante, porém por vezes controversas. A utilização de revisões sistemáticas e metanálises relacionadas aos diferentes aspectos desse tema pode contribuir para elucidar os

diferentes fatores relacionados a osseointegração e garantir um tratamento com menor risco a falhas e menor incidência de complicações.

3 ARTIGO I – Polimorfismo em metaloprotease é fator de risco para falha na osseointegração de implantes? Uma revisão sistemática e metanálise

Is polymorphism in metalloproteinases a risk factor for implant osseointegration failure? A systematic review and meta-analysis

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ABSTRACT

Objectives: This study aimed to analyze if polymorphisms of metalloproteinases can influence endosseous implants osseointegration failure.

Data Source: Electronic databases, references of reviewed articles, scholar google, and periodicals of the area of dentistry and orthopaedics.

Data Selection: Two calibrated reviewers read all titles and abstracts of the articles and selected which are related to the theme. Then, the authors reviewed the full selected articles fulfilling the inclusion and exclusion criteria.

Data Extraction: Data related to article publishing, sample size and genetic results were extracted from each study.

Data Synthesis: Three hundred and sixteen articles were screened, and nine studies were selected resulting in 5 different polymorphisms in 3 MMP genes analized in the meta-analysis. The MMP-1 g.-1607 G>GG (rs1799750) is statistically associated with osseointegration failure as a protective factor (OR=0.15, 95% CI=0.05-0.45). The MMP-8 g.-799 C>T (rs11225395) is associated with a higher risk of implant osseointegration failure (OR=3.07, 95% CI=2.02-4.67). The MMP-1 g. 3' UTR C>T (rs5854) is associated with a higher risk of implant failure only in Caucasian population (OR=6.88, 95% CI=3.48-13.59) while in Asian population is a protective factor (OR=0.35, 95% CI=0.17-0.74). Finally, the MMP-3 g.-1612 5A>6A (rs3025058) and MMP-1 g.-519 A>G (rs1144393) showed no association with osseointegration failure.

Conclusion: Our study suggests that some polymorphisms of metalloproteinases can be involved in the risk of osseointegration failure.

Keywords: Genetic Association Studies; Matrix Metalloproteinases; Genetic Polymorphism; Osseointegration; Endosseous implants

INTRODUCTION

Osseointegrated implants have been considered the most functional alternative to dentistry and orthopaedics therapy, as they can provide predictable, reproducible, and durable results. Despite the long-term success shown by longitudinal multicenter studies, failure is inevitable.

Dental and orthopaedic implants have many similarities. They are manufactured in titanium, a metal known for its good biocompatibility, resistance to mechanical fatigue and excellent osseointegration, characteristic due to its passivating oxide layer[1]. In both cases, the osseointegration process begins with an endosteal injury that occurred during implantation surgery, which induces the beginning of bone repair. This repair process involves a cascade of cellular response with the participation of several mediators, cells, and the extracellular matrix that promote the formation of new blood vessels, deposition of the extracellular matrix, and formation of tissue remodeling[2,3]. Furthermore, the patter of bone loss is similar since in dental and orthopaedic implants the process begin in the proximal area of the implant and progress to the distal part[4].

Metalloproteinases (MMPs) are a group of endopeptidase enzymes that are capable of degrading practically the entire extracellular matrix, basal membrane, and its components[5,6]. Therefore, they play an important role in the regulation of extracellular matrix homeostasis in humans[7]. These proteases are secreted by local cells and many of their biological activities are performed in an extracellular

environment, where they critically influence cell behavior. Their targets vary from degradation or proteolytic activity of the extracellular matrix molecules to growth factor peptides, cytokines, molecules cell adhesion, and many other types of receptors and glycoproteins residing on the cell surface[8,9]. MMPs play an important role in various physiological remodeling processes, such as bone remodeling, wound healing, angiogenesis, neurovascular integrity, remyelination, and restoration of connectivity[10-15] and appear to be involved in implant failure.

Although the bases of human DNA are more than 99.9% identical, sequence variations, like genetic polymorphisms (SNPs – Single Nucleotide Polymorphism) contribute to biological variation and affect how each individual responds to processes and diseases. SNPs may influence osteogenesis and inflammatory responses, explaining some of the interindividual risk factors in osseointegration.

Thus, this systematic review and meta-analysis aims to identify the contribution of SNPs in MMP genes in the risk of osseointegration failure, including dental and orthopaedic implants.

MATERIALS AND METHODS

Standardized criteria and study type

The systematic review and meta-analysis protocol was planned according to the Cochrane Handbook for Systematic Reviews of Interventions[16], as applicable, and registered in the PROSPERO (CRD42020172108). This report was written following the PRISMA checklist[17].

The analysis was performed using the PECO question: (1) population: patients who required osseointegrated implant placement; (2) exposition: polymorphisms in

MMP genes; (3) comparison: patients with implant failure vs. patients with implant success; (4) outcome: main SNP in MMP gene evaluation results for patients with implant failure. So, the PECO question answered was is polymorphism in metalloproteinases a risk factor for implant osseointegration failure?

Literature search strategy

The literature search was performed on the following databases: Pubmed/MEDLINE, EMBASE, Scielo, BVS (LILACS and BVS Odontology), and Cochrane Controlled Trials. Additionally, the gray literature and a manual search in references of reviewed articles, Scholar Google, and periodicals of specific relevance to the area of dentistry and orthopaedics were also performed. For the search terms, the Boolean operator AND and OR combined with words related to population, intervention, and outcome were used (Table 1, Suppl. 1). No filter or limit was used in the search.

In the preliminary search, two previously calibrated reviewers (RSR and AHPG) independently read all titles and abstracts of the articles and selected those related to the theme. This step was conducted in a blinded manner, and in case of any discrepancies, both authors discussed and reached a consensus. Rayyan QCRI software was used to help in the screening step.

The authors then reviewed the full selected articles fulfilling the inclusion and exclusion criteria independently and blinded. In case of any discrepancies, a third reviewer (MCLGS) provided an opinion to resolve them.

Eligibility criteria

The following inclusion criteria were applied:

(1) Study in humans;

(2) Patients who received dental and/or orthopaedics implants;

(3) Studies that evaluated metalloproteinase SNP;

(4) Case-control studies;

(5) English, Portuguese and Spanish articles.

The following exclusion criteria were applied:

(1) In vitro or animal studies;

(2) Study design other than case-control;

(3) Articles with languages other than English, Portuguese, and Spanish.

Data extraction

Data extracted from each study were analyzed and sorted, and the following standardized information was obtained: author, title, year of publication, type of implant, inclusion criteria, exclusion criteria, the ethnicity of enrolled participants, gender, average age, number of patients (control and test), number of implants and sites, follow-up time of each study, study type, and Hardy-Weinberg Equilibrium. In case additional information was needed, the authors were contacted via email..

Risk of bias in individual studies

The Newcastle-Ottawa scale was used to evaluate the quality of individual studies. This scale is used for observational studies and has a specific questionnaire for case-control studies. This instrument includes three domains: selection (maximum of four points), comparability (maximum of two points), and outcomes (maximum of three points). A low risk of bias was considered 7-9 points[18]. Two researchers (RSR and AHPG) independently assessed the risk of bias of the included studies.. In case of any discrepancies, the opinion of the third reviewer (AGS) was sought to resolve them.

Statistics

The MetaGenyo software was used to evaluate the association between MMPs SNPs and the risk of implant osseointegration failure[19]. To ensure the validity of the results, the meta-analysis was performed using also the R software with the metafor package. However, only the MetaGenyo results are presented in this article..

The P-value for Hardy Weinberg Equilibrium (HWE) was calculated for the controls. Since the analysis comprises several studies, the P-values were adjusted using the Benjamini and Hochberg false discovery rate (FDR) method of the $\chi 2$ test to reduce false positives.. Adjusted P-values greater than 0.05 indicated that the study fits with HWE conditions.

Twenty-four genes encode MMPs in humans, including duplicated MMP-23 genes and several SNPs that have already been described in MMP genes. In this study, we evaluated five SNPs in MMPs, which were the ones that the literature correlated with osseointegration.

To perform a meta-analysis, MetaGenyo (http://bioinfo.genyo.es/metagenyo/) combined the effect sizes of the included studies by weighting the data according to the amount of information in each study. Association values were calculated based on two different statistic models: Fixed Effects Model (FEM) and Random Effects Model (REM) depending on the amount of heterogeneity in the data, which was also evaluated with the heterogeneity indicator I2. I2 values above 50% were considered to indicate significant heterogeneity indicating, the use of the REM.

The forest plot was generated to summarize information for effect size and the corresponding 95% confidence interval (CI) of each study and the pooled effect. We used a recessive genetic model (AA vs. AB + BB), and an allelic contrast model (B-allele vs. A-allele), respectively (A represented major allele and B represented minor allele). To choose which comparison model to use, the genotype was analyzed to identify the allele influence in the osseointegration failure. A forest plot with these results was generated for the selected genetic model. Subgroup analysis was performed based on the ethnicity of the study population or implant type when the overall heterogeneity was above 50%.

All P-values are adjusted for multiple testing with the Bonferroni method. It was considered 0.05 as statistically significant for P-value and adjusted P-value.

A sensitivity analysis was performed by leave.one-out method, where each study was omitted each time to evaluate the influence of single studies on the overall estimate. The publication bias was not performed due to the low number of studies. No adjustment for environmental effects was performed since each study already excluded any probable environmental influence.

RESULTS

Characteristics of the included studies

A detailed flow chart of the included studies is shown in Figure 1. A total of 239 articles were rescued on the databases with no additional articles found on the other sources. After duplicate removal and title and abstract screening, thirteen studies were fully analyzed against the inclusion and exclusion criteria. Nine studies were included in the systematic review for filling all the requirements, resulting in nine polymorphic sites. However, to the meta-analysis four polymorphic sites were excluded because the data were from a single article.

Table 1 provides an overview of the included articles in the meta-analysis. Regarding the SNPs evaluated, five different SNPs were considered, including four in collagenases genes (MMP-1, MMP-8) and one in Stromelysin gene (MMP-3). These MMPs have substrates and expression in several common tissues and are capable of activating and being activated by numerous non-matrix molecules, in addition to some of them being activated by other MMPs. The primary substrates, cell types that express and the activating and activated molecules by the MMPs are summarized in Table 2.

In most studies, DNA was extracted from buccal epithelial cells, while in only two studies it was extracted from peripheral blood. Regarding the genotyping method, Polymerase Chain Reaction were used followed by restriction endonuclease digestion, dual-labeled probes in real-time PCR or fluorescence emission.

The quality assessment of case-control studies included in this systematic review and meta-analysis is shown in Table 3, and the most of the studies had a low risk of bias.

Patients and Implants

In the nine articles selected, a total of 677 patients were included, and most of them were evaluated for more than one polymorphic site, some studies evaluated the same patients. Most studies evaluated the failure of the early dental implant, at least one implant per patient, and more than 300 failure implants. Orthopaedic implant included total hip arthroplasty with at least 183 failure implants.

Dental implant success was considered evaluating implant immobility, health of periimplant tissues, function and comfort of patient. Diagnostic criteria used for the assessment of dental implant failures was presenting mobility and/or pain. Total hip arthroplasty success was considered to remain when clinically asymptomatic for more than 5 years and showed no radiographic features of aseptic loosening. Early failure was clinical, radiological, laboratory, and intrasurgical diagnosis of aseptic loosening in the first 5 years after total hip arthroplasties. Mainly was evaluated hip pain when walking or moving the joint, migration of prosthetic components or bone radiolucency around the prosthesis of more than 2 mm, and inflammatory tests within normal patterns: erythrocyte sedimentation rate, polymerase chain reaction (PCR), and leukogram.

In dental implant studies, the subjects were in good general and oral health and did not have any of the following exclusion criteria: smokers, a history of diabetes or osteoporosis, hepatitis or HIV infection, immunosuppressive chemotherapy, history of any disease known to severely compromise immune function. It also excluded patients that submitted a precocious prosthesis load or regenerative surgery, such bone grafting, and have had postsurgical complications, such as infection. All patients have a transgingival healing concept performed. In total

hip arthroplasty studies, no patients had clinical, biochemical, or operative findings suggestive of infection. Some studies indicate that patients were excluded if they had any rheumatological diseases, immunological diseases, diabetes, hepatitis, or use of immunosuppressant agents.

All studies have control and test groups age- and gender-matched patients. Dental implant patient showed average age of 49 years ± 10 (18–80), prevalence of females (65%), and prevalence of maxillary implant (61% and mean of 4.6 implants by patients). The mean follow-up time was 7 years (minimum 1 years and maximum 18 years). Total hip arthroplasty patients showed average age between 57 and 72 years and proved to be therapeutically successful over long-term follow-up (at least 10 years).

Meta-analysis results

Five SNPs were included in the meta-analysis. All of them had previously been identified and included in the database of the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP/) with minor allele frequencies greater than 0.15. The genotype distributions of all the included studies were in accordance with HWE, except for the study of Leite et al., 2008[20] and Santos et al., 2004[21] (Table 1).

The main results of the meta-analysis are shown in Table 4. The association between five SNPs and osseointegration failure was evaluated in two comparison models: recessive model and allele contrast. Subgroup analysis was performed according to the ethnicity and type of implant.

In MMP-1, three polymorphic sites were evaluated. Analyzing the MMP-1 g.-519 A>G (rs1144393) SNP the meta-analysis showed no association between this SNP and osseointegration failure (AA vs AG + GG: OR=0.80, 95% CI=0.15-4.30, p=1; A vs G: OR=0.92, 95% CI=0.45-1.88, p=1). Besides the high heterogeneity, no subgroup analysis was performed due both studies were carried out in the same population and implant type. Regarding the association between MMP-1 g.-1607 G>GG (rs1799750) SNP, both the recessive and allele contrast model in the overall analysis were statistically significant (1G1G vs 1G2G + 2G2G: OR=0.15, 95% CI=0.05-0.45, p=0.0049; 1G vs 2G: OR=0.16, 95% CI=0.05-0.53, p=0.019) (Figure 2). As the heterogeneity in the overall analysis were high (1G1G vs 1G2G + 2G2G: I2=67%, p=0.03; 1G vs 2G: I2=89%, p=0), a subgroup analysis was performed. In the stratified analysis by implant type, significant associations were observed in the dental implant (1G1G vs 1G2G + 2G2G: OR=0.28, 95% CI=0.17-0.44, p=5.302e-07; 1G vs 2G: OR=0.32, 95% CI=0.12-0.85, p=0.153) and total hip arthroplasty (1G1G vs 1G2G + 2G2G: OR=0.01, 95% CI=0.00-0.16, p=0.0095; 1G vs 2G: OR=0.05, 95% CI=0.02; 0.14, p=6.8e-09) in both models.

Both models, recessive and allele contrast, in the MMP-1 g. 3' UTR C>T (rs5854) SNP were not statistically associated with osseointegration failure in the overall analysis (CC vs CT + TT: OR=1.57, 95% CI=0.09-28.64, p=1; C vs T: OR=1.09, 95% CI=0.12-9.65, p=1). Subgroup analysis by ethnicity were performed due to the high heterogeneity in the overall (CC vs CT + TT: I2=97%, p=0; C vs T: I2=97%, p=0). Regarding the recessive model, the ethnicities Asian (CC vs CT + TT: OR=0.35, 95% CI=0.17; 0.74, p=0.038) and Caucasian (CC vs CT + TT: OR=6.88, 95% CI=3.48-13.59, p=2.059e-07) were statistically significant. In the allele contrast model, both Caucasian (C vs T: OR=3.27, 95% CI=2.21- 4.83, p=1.92e-08) and

Asian (C vs T: OR=0.35, 95% CI=0.19-0.65, p=0.005) ethnicities also showed statistical association.

The association between MMP-3 g.-1612 5A>6A (rs3025058) SNP and osseointegration failure was not statistically significant in both recessive and allele contrast models (6A6A vs 6A5A + 5A5A: OR=0.62, 95% CI=0.41-0.93, p=0.158; 6A vs 5A: OR=0.79, 95% CI=0.60-1.03, p=0.078). The multiple comparison also not show association.

Both models, recessive and allele contrast, in the MMP-8 g.-799 C>T (rs11225395) SNP were statistically associated with osseintegration failure (TT vs TC + CC: OR=3.07, 95% CI=2.02-4.67, p=1.0792e-06; T vs C: OR=2.09, 95% CI=1.53-2.87, p=2.78217e-05) (Figure 3).

Sensitivity analysis

A sensitive analysis was performed to visualize if any study has a significantly greater contribution to overall statistics than the other studies. The sensitivity analysis indicated that no individual study influenced the OR value of MMP-3 g.-1612 5A>6A (rs3025058) and MMP-8 g.-799 C>T (rs11225395) SNPs. Regarding the SNP MMP-1 g.-519 A>G (rs1144393) and MMP-1 g. 3' UTR C>T (rs5854), the studies have an opposite OR and contribute differently for the overall OR. For the MMP-1 g.-1607 G>GG (rs1799750) SNP, the pooled ORs materially altered when the studies from Munhoz et al., 2018 and Santos et al., 2014 were omitted in both genetic models in the overall comparison.

DISCUSSION

Some studies revealed the existence of clustering of implant failure[22-24], with multiple implant failure occurring in a single individual, suggesting that genetic aspects may be contributing factors. All studies evaluated in this systematic review and meta-analysis excluded patients with systemic factors that would result by themselves in a higher chance of osseointegration problems.

For example, smoking can impair bone and wound healing[25], and smokers have a 3% higher chance of losing a dental implant compared to non-smokers. A history of periodontitis may increase the risk of developing peri-implantitis and dental implant loss[25]. Radiotherapy and radiochemotherapy profoundly modify the oral environment, leading to xerostomia, changes in anatomy and reduced perfusion of hard and soft tissues, representing a challenge to the process of osseointegration of dental implants[26,27]. The younger age and avascular necrosis are risk factors that could increase the occurrence of aseptic loosening of the total hip implant[28]. The higher incidence of aseptic loosening in young patients is probably due to the greater wear and tear and generation of debris caused by the higher level of physical activity in this age group. Cases of loosening due to periprosthetic fractures were excluded from the study since creating areas that lead to the loosening of the implant, may have been generated by wear of the same and by the time of arthroplasty, which would generate a bias in the work. Also, there is a correlation between high inflammatory activity in a patient with rheumatological disease and an increased risk of aseptic loosening[29]. Thus, all studies evaluated in this meta-analysis presented strict sample selection criteria, reducing the interference of risk factors that could mask or increased the real role of SNPs.

Another important point is the necessity to treat types of implant failure as distinct events when attempting to characterize risk factors, including genetic risk. The mechanism of failure in early and late implant loss is distinct, as early implant loss represents a failure in the osseointegration process, whereas in late implant loss osseointegration has already occurred. In addition, aseptic failure has particular characteristics, with aseptic loosening being the major cause of all total hip arthroplasty failures due to aseptic inflammatory reactions to prosthetic implants. All studies evaluated in this systematic review and meta-analysis selected early and aseptic loss, when the implant stimulates mesenchymal cells to inflammatory response and osteoclast accumulation, leading to excessive resorption, bone loss, and periprosthetic osteolysis[30,31].

With these selection criteria, associations between different MMP SNPs and implant failure were found in the meta-analysis. The MMP-1 g.-1607 G>GG (rs1799750) in an overall analysis showed association with osseointegration failure as the recessive genotype also protects the patient. As the heterogeneity was high, a subgroup analysis was performed and, the SNP was still associated with both dental and total hip implant failure. This SNP is located in the promoter region of the MMP gene and is related to the expression and activity of the MMP-1 enzyme[32], since the GG allele increases the transcriptional activity. MMP-1 enzyme is a collagenase involved in the tissue remodeling process, cleaving fibrillar collagen type I, II and III into characteristic 3/4 and 1/4 fragments[6]. Thus, a change in the MMP-1 expression or activity due to the presence of a specific allele in this SNP could explain a more intense degradation of collagen interfering significantly in the osseointegration process.

Indeed, according to the literature, there is a correlation between MMP-1 g.-1607 G>GG (rs1799750) SNP and collagen and/or bone pathologies. Studies associate this SNP with osteoarthritis in the younger population[33] and the development of temporomandibular joint osteoarthritis and osteoarthritis in people aged less than 60 years[34]. BARONEZA et al. (2014)[35] showed that MMP-1 g.-1607 G>GG (rs1799750) SNP is associated with posterior tibial tendon insufficiency. It was also found that this SNP is associated with a higher risk to have a rotator cuff tear injury[32], knee osteoarthritis[36-38] and osteomyelitis[39]. In addition, oral and oropharyngeal squamous cell carcinoma when associated with tobacco and alcohol had also a relationship with this SNP[40]. So MMP-1 g.-1607 G>GG (rs1799750) SNP appears to be a significant genetic risk marker in musculoskeletal processes.

The MMP-1 g.-519 A>G (rs1144393) showed no association with osseointegration failure, corroborating with the literature, where no associations were found in other oral health conditions and chronic periodontitis[41-43]. However, this SNP was associated with risk of development of osteomyelitis[39] and tendinopathy[35,44]. Confirming the important role of MMP-1 in the pathobiology of collagen and suggesting that each SNP must be carefully evaluated in different pathological events.

Finally, in the overall analysis, the MMP-1 g. 3' UTR C>T (rs5854) also did not show any association. However, in the subgroup analysis by ethnicity, an association was found in Caucasian and Asian ethnicities suggesting that in the Caucasian population the recessive genotype is involved in a higher risk of osseointegration failure, and in the Asian population, the recessive genotype protects from the osseointegration failure. This can explain why the overall analysis did not show statistical significance and confirms the importance of an allele-specific investigation

in each ethnic group. Studies with this SNP are rare in the literature, but one study showed that a person with this SNP has a higher chance to develop oral squamous cell carcinoma[45].

The studies that analyzed the SNP MMP-3 g.-1612 5A>6A (rs3025058) showed that this SNP is not related to the osseointegration failure which is corroborated by the results of this meta-analysis that showed no statistical significance when Bonferroni correction is applied.

The MMP-3 g.-1612 5A>6A (rs3025058) SNP is an insertion or deletion of adenosine in the promoter region of the MMP-3 gene in the position -1612. This change generates a binding for a transcription factor that modifies the MMP-3 transcription. The presence of the 5A allele increases the MMP-3 activity twice, which interferes with the MMP function in the connective tissues[46]. This SNP was associated with the decreased susceptibility to chronic periodontitis, especially in Asian populations and decrease of the risk of aggressive periodontitis in Asians[47]. On the other hand, MMP-3 g.-1612 5A>6A (rs3025058) SNP was related to a higher risk for anterior cruciate ligament injury in a sporting population[48] and increase the susceptibility to develop oral submucous fibrosis and head and neck squamous cell carcinoma[49].

The meta-analysis showed that the recessive genotype of the MMP-8 g.-799 C>T (rs11225395) SNP is involved in a higher risk of osseointegration failure. There are a few studies in the scientific literature with this SNP and two of them showed an association with posterior tibial tendon insufficiency and pathogenesis of atherosclerosis[44,50]. Moreover, WENG at al. (2016)[51] performed a meta-analysis and found a higher risk to develop periodontitis when an MMP-8 g.-799 C>T (rs11225395) SNP is present and it is known that untreated periodontitis can

culminate in a dental implant loss. Accordingly, the MMP-8 is involved in periodontal destruction because of its activity of collagenase. This relationship can explain why patients with a SNP in MMP-8 have more risk to develop implant failure[6,52,53].

Most of the evidence from our study should be considered stable and convincing. However, some potential limitations still exist that need to be addressed. Firstly, a relatively large heterogeneity was evident in this meta-analysis. Nevertheless, through stratified analysis by ethnicity and type, heterogeneity reduced significantly. In fact, the genotype distributions of SNPs vary in different ethnics and must be evaluated carefully. Besides that, publication bias is inevitable because only English, Spanish and Portuguese articles were included. Therefore, it is possible that some relevant studies published in other languages were not included, which might introduce publication bias.

Finally, in our meta-analysis, a relatively small number of studies and polymorphic sites were used, showing the scarce literature in this area. It is important to include more studies in different populations to better understand the role of MMP SNPs in implant failure..

Despite these limitations, the data from this meta-analysis can guide the genetic identification of individuals at higher risk of implant failure and contribute to strategies for modulating genetic markers to ensure personalized therapy..

CONCLUSION

In summary, this meta-analysis has shown that the presence of the MMP-8 g.-799 C>T (rs11225395) SNP is associated with a higher risk of osseointegration failure. The MMP-1 g. 3' UTR C>T (rs5854) SNP is linked to a higher risk of

osseointegration failure in Caucasian populations, while the Asian population appears to act as a protection factor.. On the other hand, MMP-1 g.-1607 G>GG (rs1799750) is a SNP that protects the person from osseointegration failure. Lastly, the MMP-1 g.-519 A>G (rs1144393) and MMP-3 g.-1612 5A>6A (rs3025058) did not show any association with osseointegration failure.

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Table 1. Characteristics of studies included in the meta-analysis

Polymorphism	First author	Year	Ethnicity	Country	Implant type	Sample Size	Genotype Cases			Genotype Controls			HWE	Adjusted HWE
							AA	*AG*	*GG*	*AA*	*AG*	*GG*		
MMP-1 g.-519 A>G (rs1144393)	Munhoz, F.B.A.	2018	Latin American	Brazil	Dental Implant	200	46	39	15	32	55	13	0.158	0.316
	Leite, M.F.F	2008	Latin American	Brazil	Dental Implant	104	7	30	7	22	30	8	0.6556	0.6556
							1G1G	*1G2G*	*2G2G*	*1G1G*	*1G2G*	*2G2G*		
MMP-1 g.-1607 G>GG (rs1799750)	Munhoz, F.B.A.	2018	Latin American	Brazil	Dental Implant	200	33	58	9	63	31	6	0.4144	0.4144
	Godoy-Santos, A.L.	2009	Latin American	Brazil	Total Hip Implant	58	0	9	18	21	7	3	0.076	0.1013
	Leite, M.F.F	2008	Latin American	Brazil	Dental Implant	104	15	24	5	37	16	7	0.0252*	0.0504
	Santos, M.C.L.	2004	Latin American	Brazil	Dental Implant	46	0	0	20	16	3	7	0.0002*	0.0008*
							CC	*CT*	*TT*	*CC*	*CT*	*TT*		
MMP-1 g. 3' UTR C>T (rs5854)	Yan, Y.	2014	Asian	China	Total Hip Implant	144	36	18	9	64	14	3	0.0699	0.1398
	Malik, M.H.A	2007	Caucasian	England	Joint Implant	235	38	34	15	15	72	61	0.3488	0.3488
							6A6A	*6A5A*	*5A5A*	*6A6A*	*6A5A*	*6A6A*		
MMP-3 g.-1612 5A>6A (rs3025058)	Munhoz, F.B.A.	2016	Latin American	Brazil	Dental Implant	240	29	67	24	40	58	22	0.9034	0.9034

	Munhoz, F.B.A.	2018	Latin American	Brazil	Dental Implant	200	26	54	20	37	45	18	0.5074	0.9034
						TT	*TC*	*CC*	*TT*	*TC*	*CC*	*TT*		
MMP-8 g.-799 C>T (rs11225395)	Munhoz, F.B.A.	2018	Latin American	Brazil	Dental Implant	200	63	25	12	36	48	16	1	1
	Costa-Junior, F.R.	2013	Latin American	Brazil	Dental Implant	180	51	20	9	36	48	16	1	1

HWE Hardy-Weinberg Equilibrium; *statistically significant $p < 0.05$.

Table 2. Characteristics of MMP included in the systematic review and meta-analysis.

Type	Primary Substrates	Cell types that express	Activating molecules	Activated molecules
MMP-1 Colagenase-1	collagen I, II, III, VII, VIII, X, aggrecan, entactin, gelatin, L-selectin, MBP, serpins, TNF precursor, versican, α-2 macroglobulin.	chondrocytes, fibroblasts, hepatocytes, keratinocytes, macrophages, osteoblast.	kallikrein, kinase, MMP-3, MMP-10, plasmin.	MMP-2
MMP-3 Estromelisina-1	collagen III, IV, V, IX, X, aggrecan, elastin, entactin, fibrillin, fibronectin, gelatin, laminin, MBP, nidogen, perlecan, tenascin, TNF precursor, versican.	chondrocytes, fibroblasts, mammary gland, macrophages, neutrophils and keratinocytes.	cathepsin G, elastase, kallikrein, kinase, plasmin, tryptase.	MMP-1, MMP-8, MMP-9, MMP-13
MMP-8 Colagenase-2	collagen I, II, III, VII, VIII, X, aggrecan, fibronectin, gelatin, laminin, serpins, α-2 macroglobulin.	Neutrophils.	MMP-3, -10, plasmin.	-

Adapted from MACIEJCZYK et al., 2016.

Table 3. Quality assessment of studies included in this systematic review using the Newcastle-Ottawa Scale.

Authors	Year	Selection	Comparability	Exposure	Total
Munhoz et al.	2019	★★	★★	★★★	7
Munhoz et al.	2018	★★	★★	★★★	7
Munhoz et al.	2016	★★	★★	★★★	7
Yan et al.	2014	★★	★★	★★★	7
Costa-Junior et al.	2013	★★	★	★★★	6
Godoy-Santos et al.	2009	★★	★	★★★	6
Leite et al.	2008	★★	★	★★★	6
Malik et al.	2007	★★	★★	★★★	7
Santos et al.	2004	★★	★	★★★	6

Table 4. Results of the overall and stratified meta-analysis

Polymorphism	Genetic model	Group/subgroup	Heterogeneity test		Statistical Model	Test for overall effect	
			I^2	P_{het}		OR (95% CI)	*p*
MMP-1 g.-519 A>G (rs1144393)	AA vs (AG + GG)	Overall	89%	0	R	0.8048 [0.1507; 4.2980]	1
	A allele vs G allele	Overall	77%	0.04	R	0.9197 [0.4498; 1.8809]	1
MMP-1 g.-1607 G>GG (rs1799750)	1G1G vs (1G2G + 2G2G)	Overall	67%	0.03	R	0.1483 [0.0492; 0.4474]	0.0049*
		Dental Implant	48.95%	0.141	F	0.2778 [0.1742; 0.4431]	5.302e-07*
		Total Hip Implant	N/A	N/A	F	0.0089 [0.0005; 0.1602]	0.0095*
	1G allele vs 2G allele	Overall	89%	0	R	0.1616 [0.0490; 0.5324]	0.019*
		Dental Implant	77.92%	0.11	R	0.3182 [0.1196; 0.8465]	0.153
		Total Hip Implant	N/A	N/A	F	0.0531 [0.0207; 0.1360]	6.8e-09*
MMP-1 g. 3' UTR C>T (rs5854)	CC vs (CT + TT)	Overall	97%	0	R	1.5654 [0.0856; 28.6400]	1
		Asian	N/A	N/A	F	0.3542 [0.1704; 0.7360]	0.038*
		Caucasian	N/A	N/A	F	6.8762 [3.4783; 13.5934]	2.059e-07*
	C allele vs T allele	Overall	97%	0	R	1.0865 [0.1224; 9.6456]	1
		Asian	N/A	N/A	F	0.3521 [0.1919; 0.6461]	0.005*
		Caucasian	N/A	N/A	F	3.2690 [2.2124; 4.8301]	1.92e-08*
MMP-3 g.-1612 5A>6A (rs3025058)	6A6A vs (6A5A + 5A5A)	Overall	0%	0.88	F	0.6188 [0.4097; 0.9346]	0.158
	6A allele vs. 5A allele	Overall	0%	0.87	F	0.7870 [0.6029; 1.0272]	0.546
MMP-8 g.-799 C>T (rs11225395)	TT vs (TC + CC)	Overall	0%	0.94	F	3.0733 [2.0206; 4.6744]	1.0792e-06*
	T allele vs C allele	Overall	0%	0.90	F	2.0938 [1.5296; 2.8662]	2.78217e-05*

*After Bonferroni correction, statistically significant $p < 0.05$.

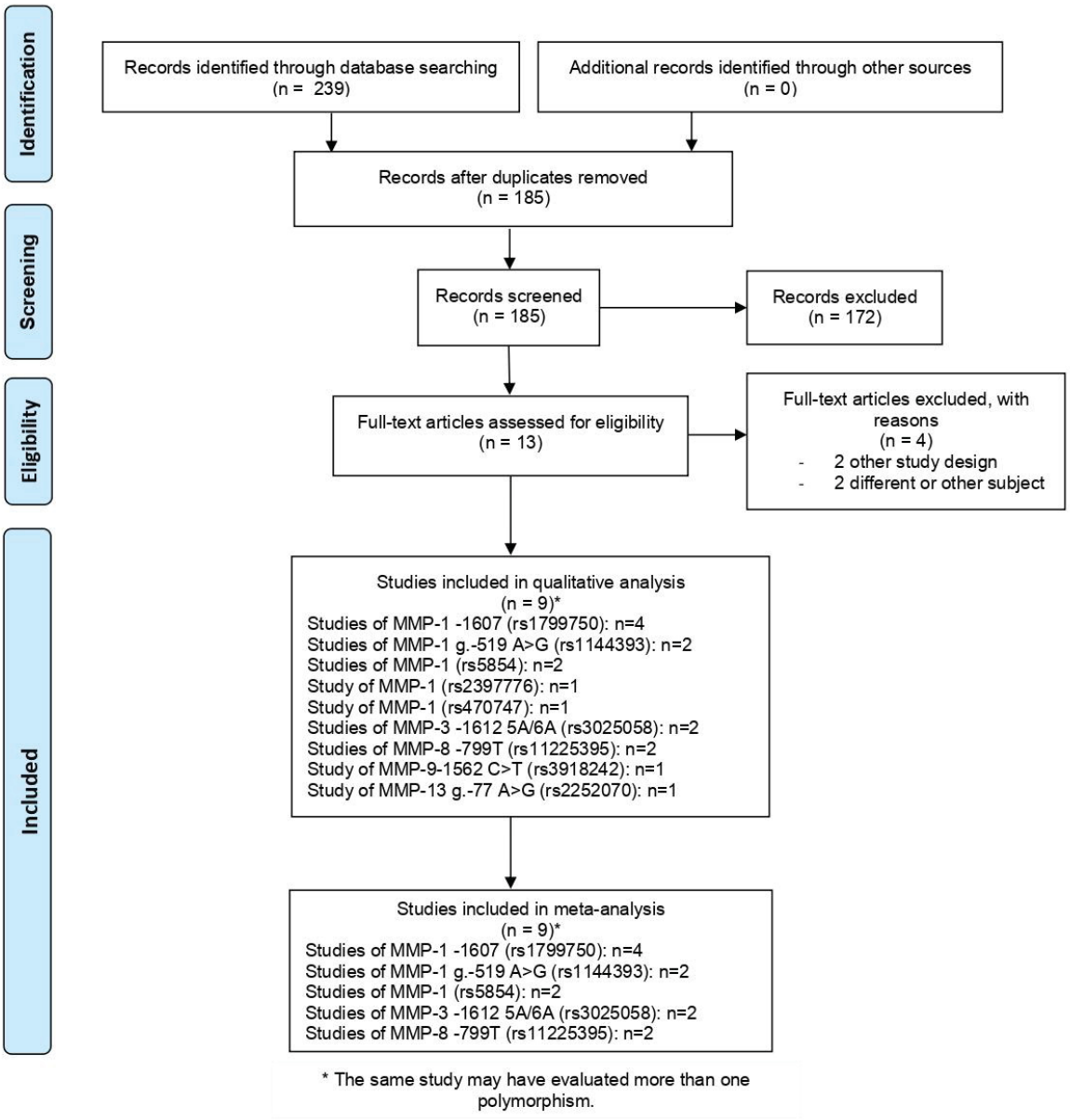
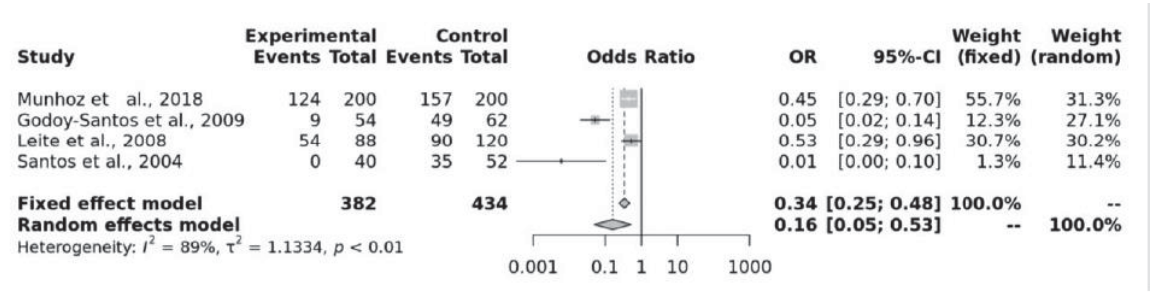
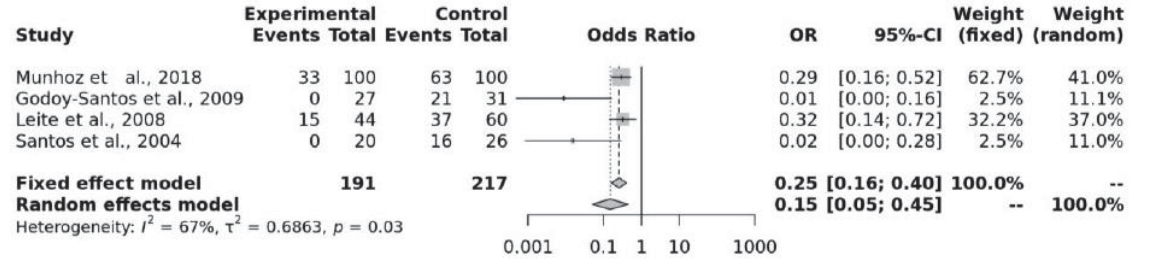


Figure 1. PRISMA flow diagram



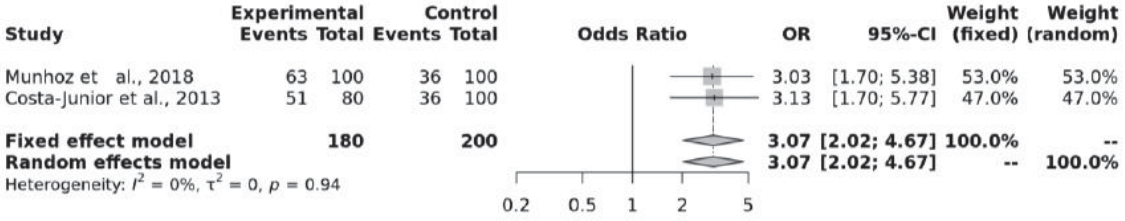
a



b

Figure 2. a) Forest plot for the association between osseointegration failure and MMP-1 g.-1607 G>GG (rs1799750) polymorphism in allele contrast comparison. b) Forest plot for the association between osseointegration failure and MMP-1 g.-1607 G>GG (rs1799750) polymorphism in the recessive model. The analyses were based on the number of patients that had had implant failure.

a



b

Figure 3. a) Forest plot for the association between osseointegration failure and MMP-8 g.-799 C>T (rs11225395) polymorphism in allele contrast comparison. b) Forest plot for the association between osseointegration failure and MMP-8 g.-799 C>T (rs11225395) polymorphism in the recessive model. The analyses were based on the number of patients that had had implant failure.

4 ARTIGO II – Comparação da taxa de sinusite após procedimento de levantamento de seio e cirurgia de implante zigomático: uma metanálise

Comparison of sinusitis rate after sinus lift procedure and zygomatic implant surgery: a meta-analysis.

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ABSTRACT

Purpose: To evaluate and compare the reported sinusitis occurrence after the sinus lift procedure and zygomatic implant placement.

Methods: This meta-analysis has been registered at PROSPERO. Studies were searched on six databases. Two authors screened titles and abstracts and fully analyzed the studies against the inclusion and exclusion criteria. The RoB 2.0 and the ROBINS-I tools were used to assess the quality and risk of bias of the included studies. The random-effects model was used for the meta-analysis. The prevalence of sinusitis was calculated based on the total of patients. Subgroup analysis was performed by sinus lift or zygomatic implant surgery technique.

Results: The search identified 2419 references. After applying the inclusion criteria, 18 sinus lift and 9 zygomatic implant placement studies were considered eligible. The pooled prevalence of sinusitis after sinus lift procedure was 1.11% (95% CI 0.30-2.28). The prevalence after zygomatic implant placement was 3.76% (95% CI 0.12-10.29). In the subgroup analysis, the lateral window approach showed a prevalence of sinusitis of 1.35% (95% CI 0.34-2.8), the transcrestal technique of 0.00% (95% CI 0.00-3.18), and the SALSA technique of 1.20% (95% CI 0.00-5.10). Regarding to the techniques for zygomatic implant placement, the sinus slot technique showed a prevalence of 21.62% (95% CI 9.62-36.52), the intrasinus technique of 4.36% (95% CI 0.33-11.08), and, the prevalence after the extrasinus technique was 0.00% (95% CI 0.00-1.22).

Conclusion: The sinusitis occurrence rate was higher after zygomatic implant placement than after sinus lift procedure and this occurrence was different depending on the used technique.

Keywords: Maxillary Sinusitis; Sinus Floor Augmentation; Zygomatic Implants; Dental Implants; Complications.

INTRODUCTION

Maxillary atrophy is a result of progressive bone loss usually caused by tooth loss, tumor resections, or trauma [1]. This is a variable and unpredictable phenomenon that jeopardize patients´ oral function. Moreover, it represents a challenge for the surgeons since bone resorption can also lead to an approximation of alveolar ridges and anatomic structures, preventing implant placement [2]. Since implant stability is crucial for implant success, bone volume availability is vital for its achievement [3].

Some approaches and techniques have been developed to rehabilitate patients with atrophic maxilla. For the last three decades, procedures such as sinus floor elevation, also known as sinus lift, have been applied prior or at the same time of implant placement as a standard treatment for the severely absorbed maxilla [1]. The sinus lift is indicated for the rehabilitation of totally edentulous patients or in cases that posterior maxillary teeth loss led to sinus pneumatization, reducing vertical bone height [3]. Currently, the most applied techniques in order to lift the maxillary sinus floor and create appropriate bone height for implants placement are lateral window and transcrestal techniques. These techniques can be performed in conjunction with bone grafting procedures and may culminate in complications such as sinusitis [4].

In 1998, Branemark introduced a new alternative for rehabilitation of patients with atrophic maxilla, through the placement of zygomatic implants (ZIs). These are long implants anchored in the zygomatic bone to support full-arch prostheses, which have been reported as a good and effective option to restore oral function [5], with high survival and success rates [6]. ZIs can be placed through different surgical techniques that usually depend on patients´ anatomy. Those are classic intrasinus, sinus slot [7], and extrasinus techniques [8]. Regarding complications, as well as in patients submitted to sinus lift, sinusitis is the most common one [9].

For the European rhinology societies, sinusitis is characterized by inflammation and swelling of the nasal and paranasal mucous membranes that lead to signs and symptoms such as purulent nasal discharge, nasal obstruction, headache, and facial and/or dental pain [10]. Since its occurrence as a result of the aforementioned procedures has been widely reported, this meta-analysis aims to

evaluate the reported sinusitis occurrence related to sinus lift and zygomatic implants.

MATERIALS AND METHODS

This review followed PRISMA guidelines [11] for conducting and reporting systematic reviews and meta-analyses. The review protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) under the code CRD42020198200.

The PICO question was defined as: “Is the incidence of sinusitis lower in patients who had a zygomatic implant placed than in patients who underwent the sinus lift procedure?”.

Literature search strategy and eligibility criteria

Searches were performed in the following databases: US National Library of Medicine (Pubmed/MEDLINE), Excerpta Medica Database (EMBASE), Scientific Electronic Library Online (SCIELO), BVS (LILACS e BBO-Odontologia), and Cochrane Controlled Trials Database. Not indexed studies and theses were searched in the Scholar Google and gray literature.

A direct search was also performed in the bibliography of all articles reviewed and in the website of scientific journals related to odontology (Clinical Implant Dentistry and Related Research, Clinical Oral Implants Research, International Journal of Oral and Maxillofacial Implants, International Journal of Oral and Maxillofacial Surgery, Journal of Clinical Periodontology, Journal of Dentistry, Journal of Oral and Maxillofacial Surgery, Journal of Oral Implantology, Journal of Oral Rehabilitation, Journal of Periodontology, and Periodontology 2000).

For the database search, a combination of MESH terms and synonyms related to the PICO question and Boolean Operators (AND, OR, NOT) was used (Table 1). Yale Mesh Analyzer, PubReMiner, and Systematic Review Accelerator software were used to help in the choice of the terms.

The screening of titles and abstracts was carried out by two researchers using the Ryyan QCRI software. Disagreements were arbitrated by a third author. After the screening, all included articles were fully analyzed against the inclusion and

exclusion criteria by two authors (Table 2). In case of any discrepancies, it was resolved by the opinion of a third author.

Data extraction

Two independent authors extracted the data in an Excel spreadsheet. Data of interest were extracted based on the general study characteristics (authors and year of publication, number of participants), surgical procedure (number of sinus lifted, type of procedure - technique, bone graft), trans and postoperative complications (types of complications and number of occurrence of sinusitis) implant characteristics (implant survive and follow-up period after implant placement).

Quality assessment of included studies

The evaluation of the study's quality was performed by two independent authors and any disagreement was resolved by a consensus. The risk of bias of randomized clinical trials (RCT) was assessed using the Cochrane Risk of Bias tool (RoB 2.0) [12] and the Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) [13] tool was used for observation studies and non-randomized clinical trials.

Statistical Analysis

The meta-analysis was performed using R program, version 3.6.2 with RStudio 2021.09.0 (R Core Team, 2018) using the meta package [14,15]. The random-effects model was used for the meta-analysis [16]. The pooled prevalence estimate of sinusitis (at 95% confidence intervals) was presented as a percentage ((number of cases of sinusitis/total of patients or sinus tested)*100) and the Freeman–Tukey double arcsine method was used to stabilize the variance. The prevalence of sinusitis was calculated based on the total of patients.

Cochran’s Q test was used to the heterogeneity between the studies and the I2 statistic for evaluation of true variation due to heterogeneity [17,18]. The I2 shows the proportion of the variance, ranging from 0% to 100%, and observes the true size effect from all studies in the analysis [18]. Subgroup meta-analysis was used to

evaluate possible sources of heterogeneity. Subgroup analysis was performed by sinus lift or zygomatic implant surgery technique. For subgroup analysis, articles with no information of used technique or refer more than one technique used and did not separate how many patients used each technique were excluded.

Possible publication bias was assessed using Egger's test in combination with a funnel plot and was visualized using funnel plots when at least ten articles were presented. The publication bias was performed only if at least ten articles was presented [19]. In all analyses, a p-value less than 0.05 was considered statistically significant.

RESULTS

Results of the Search and Selection of Studies

A detailed flow diagram of the screening and inclusion procedure is shown in Figure 1. A total of 2419 articles were retrieved from the databases (sinus lift = 2160; zygomatic = 259). Thirty-seven articles were rescued through other sources (sinus lift = 8; zygomatic = 29). After duplicates removal, 2170 articles were screened and, 215 full text were assessed against the eligibility. Finally, 27 articles were included in the quantitative analysis (sinus lift = 18; zygomatic = 9).

Characteristics of the Included Studies

Characteristics of sinus lift studies included are shown in Table 3. One thousand ninety-five patients were followed by the studies and at least 1441 sinus were lifted. Regarding the sinus lift technique used, 15 studies used the lateral window technique, 2 the transcrestal technique and 1 SALSA technique.

The implant's survival varied from 89% to 100% in up to 22 years of follow-up. Trans- and postoperative complications occurred in the majority of studies, the most cited were maxillary sinusitis, sinus membrane perforation, implant failures, wound dehiscence, bleeding and others. Twenty occurrence of sinusitis were observed

Characteristics of zygomatic studies are shown in Table 4. Two hundred eighty-two patients have received zygomatic implants together or not with bone graft. The implant's survival rate varied from 90.9% to 100% in up to 72 months of follow-

up. The zygomatic implants were placed through intrasinus, sinus slot, and extrasinus techniques being the intrasinus the most used. The most cited trans- and postoperative complications were maxillary sinusitis, implant failure, pain, fistula, oroantral communication among others. Sixteen occurrences of sinusitis were observed.

Assessment of Methodological Quality

The risk of bias of observational studies is shown in Figure 2 for sinus lift studies. In general, the studies have low risk in isolated points, being the most critical points confounding, selection, and measurement of outcome bias. However, when evaluated together the overall risk of bias is serious. For zygomatic studies the overall risk of bias shows serious and critical risks (Figure 3).

Regarding the randomized studies, the risk of bias is shown in Figure 4 for sinus lift studies. All studies had some concerns but none of them had high risk. Concerns are related to the randomization process, measurement of the outcome, and selection of reported results.

Meta-analysis

The pooled prevalence of sinusitis after sinus lift procedure in 18 studies using the meta-analysis of the random-effects model was 1.11% (95% CI 0.30-2.28) (Figure 5). The overall estimated prevalence showed a medium heterogeneity (I^2 = 33%). Regarding the prevalence of sinusitis after zygomatic implant surgery in 9 studies, the meta-analysis of the random effects model showed a prevalence of 3.76% (95% CI 0.12-10.29). The overall estimated prevalence showed a high heterogeneity (I2 = 74%) (Figure 6).

In the subgroup analysis related to the technique used to perform the sinus lift, the lateral window approach showed a prevalence of sinusitis of 1.35% (95% CI 0.34-2.8) with medium heterogeneity (I^2 = 43%) in 15 studies. The transcrestal technique showed a prevalence of 0.00% (95% CI 0.00-3.18) with no heterogeneity (I^2 = 0%) in 2 studies. The SALSA technique showed a prevalence of 1.20% (95% CI 0.00-5.10) in 1 study (Figura 5).

The sinusitis prevalence regarding different zygomatic implant surgery techniques was also evaluated by subgroup analysis. The sinus slot technique showed a prevalence of 21.62% (95% CI 9.62-36.52) in 1 study. The intrasinus technique showed a prevalence of 4.36% (95% CI 0.33-11.08) with medium heterogeneity (I^2 = 35%) in 6 studies. Lastly, the prevalence after extrasinus technique was 0.00% (95% CI 0.00-1.22) with no heterogeneity (I^2 = 0%) in 2 studies (Figura 6).

No apparent asymmetry in the funnel plot was observed and the absence of evidence of suspected publication bias was supported by Egger's statistical test in relation to sinus lift procedure (p = 0.0676) (Figure 7). For zygomatic implant surgery, due to the number of studies, it was not possible to perform the publication bias.

DISCUSSION

Many complications after sinus lift and zygomatic implant surgery were reported in the selected studies: sinus membrane perforation, wound dehiscence, bleeding, pain, infection, facial edema, graft failure, fistula, orosinusal communication, and hematoma. These finds are consistent with the literature [20-22].

Another complication cited in selected studies is implant failure. In the studies included in this meta-analysis, the survival rate after the sinus lift procedure ranged from 89 to 100% in up 22 years of follow-up to while after zygomatic implant surgery was between 90.9 to 100% in up to 72 months of follow-up. The survival rates reported in this meta-analysis are even better that the literature which describes a survival rate ranging between 81.8% to 100% for sinus lift in up to 4 years of follow-up [23-28] and 77% to 100% for zygomatic implants in up to 11.7 years of follow-up [6,20,29-33].

One of the main complication after sinus lift and zygomatic implant placement is sinusitis. In this meta-analysis, the sinusitis rates after both procedures were low: 1.11% after sinus lift procedure and 3.76% after zygomatic implant placement. Active sinusitis before sinus lift and zygomatic implant surgery was an exclusion criteria in this meta-analysis to eliminate the confounding related to exacerbation of a previous chronic sinus condition and to validate this association with study design restricted.

It has been reported that the zygomatic implant acting as foreign body, anatomic conditions and variables of the surgical technique may be related to

sinusitis development [9]. Perforation of the sinus membrane and leakage at the level of the maxilla caused by the surgery, which leads to migration of bacteria from the mouth to the sinus, seem to be critical factors for this complication [34]. On the other hand, although membrane perforation can occur in sinus lift procedures, small perforations do not seem to be related to postoperative sinusitis [35]. Moreover, the lateral window approach with submerged implants that are not exposed to the maxillary sinus, and the use of thinner allograft material, have been reported to be safer with respect to sinus complications [36].

However, it is important to emphasize that the zygomatic implant may be the technique of choice in some situations, as for patients with the severely atrophic maxilla, with the necessity of extensive bone grafting and larger surgical time and consequently higher patient morbidity. In this case, zygomatic implants appear as an advantageous alternative for patients with the severely atrophic maxilla, who had bone graft failure in the past, and/or who have severe medical issues, which preclude extensive surgical [37].

Despite the greater risk to sinusitis after zygomatic implant placement other factors must be considered: the reduction on surgical sites, fewer numbers of surgical procedures, the reduction of time between implant placement and final prosthesis delivery, and less invasiveness compared to extensive bone grafting. In addition, sinusitis after the zygomatic procedure is generally solved favorably and without major problems after the use of antiseptic, antibiotics, and/or corticosteroids [38]. So, some aspects must be considered in planning rehabilitation.

This meta-analysis suggest that the sinusitis rate is different depending on the surgical technique used. The lateral window technique was the most frequent in the studies included in this meta-analysis (83.3% of studies) and showed a low rate of sinusitis. According to the Sinus Consensus Conference of 1996 [39], the lateral window technique for sinus lift is recommended when the residual bone height is between 1 to 6 mm . Thus, this technique is preferred over transcrestal sinus lift, when a higher amount of augmentation is necessary [3]. However, this study shows that the lateral window approach has a higher rate of sinusitis that the transcrestal technique. The lateral window technique is a relatively large surgical procedure, more invasive than transcrestal and the procedure of opening the window can enhance the possibility of maxillary membrane perforation, a complication frequently cited in the literature [40] and that can predispose to sinusitis.

The transcrestal technique showed a sinusitis rate lower than lateral window, which fit with the clinical observation since the transcrestal is a less invasive technique recommended when the residual bone height is between 7 to 9 mm [39]. An important observation is that only 2 studies using the transcrestal technique were included in the criteria of this meta-analysis and in both of them no case of sinusitis was reported. Thus, more studies are needed to assess the frequency of sinusitis with this technique.

Although the SALSA technique presented a sinusitis rate similar to the lateral window, only one study used this technique, which is a small sample. Thus, it is important to confirm these results with further studies related to both techniques.

Regarding zygomatic implant placement, the intrasinus technique was the most frequent in the studies included in this meta-analysis and showed a higher rate of sinusitis than extrasinus. This is expected since to perform the intrasinus technique is necessary to open a lateral wall and in most cases elevate the maxillary sinus membrane, which can lead to membrane perforation [41], predisposing other complications. In addition, in the extrasinus technique there is a reduced possibility of oroantral communication and an improvement in the implant position for prosthesis placement [1], suggesting that this technique shows lower risk of trans- and postoperative complications.

Even though the sinus slot technique presented the highest sinusitis rate, this should be interpreted with caution, because only one study used this technique. More studies using the sinus slot technique are necessary to confirm this sinusitis rate. However, the authors suggest that because of its less invasiveness when compared with intrasinus technique, this technique lead to less sinusitis rate.

It is important to highlight that the zygomatic technique depends on the patient's zygoma bone anatomy. According to Moro et al. (2021) [42], among 268 patients with edentulous maxilla, 34.95% have had a small concavity sizes, 52.30% medium, and 7.35% large. Which indicated that less patients would benefit from the extrasinus technique being in most of them possible to place the implant though the sinus slot technique [42].

One observed concern is about the evaluation of sinusitis. There is not a consensus on how to evaluate and report sinus state. Objective diagnosis tolls (endoscopy) and image (computed tomography) are the most sensitive and specific methodologies to evaluate sinusitis [43]. Thus, the best way is to perform an

exhaustive radiological and clinical analysis. However, there is a lack of standardization in sinusitis diagnosis between the included studies, which can interfere with the results. Therefore, the authors reinforce the necessity of standardization and adherence to clinical practice guidelines already established such as the guideline from the American Academy of Otolaryngology–Head and Neck Surgery (AAO-NHS).

In general, the studies included in this meta-analysis have a serious or critical bias, which is already expected in observational studies since it is difficult to control potential confoundings in this type of study design. The present review was planned to summarize the current evidence but without excluding the most biased studies. Thus, the authors suggest that more randomized clinical trials should be performed and particularly related to the specific evaluation of occurrence of sinusitis after both procedures, sinus lift and zygomatic implant placement.

Another important issue is that meta-analysis are normally performed with randomized 2-arm studies. As most studies evaluated in this meta-analysis are observational, the method chosen was adapted to use the kind of date available. Also, as there is no randomized study directly comparing the sinusitis rate between sinus lift and zygomatic procedures or techniques. Thus, the authors suggest that more comparable studies should be performed.

This study contributes to the clinician in the selection of the best surgical techniques in case of maxillary atrophy and compromised bone space, mainly in patients with a preview history of sinusitis. Furthermore, knowing the sinusitis rate is important to guide the patient about this possibility after treatment.

CONCLUSION

In conclusion, the rate of sinusitis after sinus lift was 1.11% and after zygomatic implant was 3.76%. More invasive techniques such as lateral window for sinus lift and intra-sinus for zygomatic implant placement lead to a higher rate of post-surgery sinusitis.

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Table 1 – Search terms used in each database.

Sinus lift	
Database	*Search terms*
Pubmed/Medline	((“atrophy”[MeSH Terms]) OR (“bone resorption”[MeSH Terms])) OR (“dental implants”[MeSH Terms])) OR (“dental implantation”[MeSH Terms])) OR (“dental prosthesis”[MeSH Terms])) OR (“maxilla”[MeSH Terms])) OR (“jaw, edentulous”[MeSH Terms])) OR (“maxillary sinus”[MeSH Terms])) OR (“jaw”[MeSH Terms])) OR (“atrophy/surgery”[MeSH Terms])) OR (“bone resorption/physiopathology”[MeSH Terms])) OR (“maxilla/surgery”[MeSH Terms])) OR (“jaw, edentulous/rehabilitation”[MeSH Terms])) OR (“atrophy”[All Fields])) OR (“bone resorption”[All Fields])) OR (“dental implants”[All Fields])) OR (“dental implantation”[All Fields])) OR (“dental prosthesis”[All Fields])) OR (“maxilla”[All Fields])) OR (Jaw, edentulous)) OR (“maxillary sinus”[All Fields])) OR (“jaw”[All Fields])) OR (“atrophies”[All Fields])) OR (“bone resorptions”[All Fields])) OR (“dental implant”[All Fields])) OR (“surgical dental prosthesis”[All Fields])) OR (“dental prosthesis implantation”[All Fields])) OR (“surgical dental treatment”[All Fields])) OR (“maxillary bone”[All Fields])) OR (“maxillae”[All Fields])) OR (“edentulous jaw”[All Fields])) OR (“edentulous jaws”[All Fields])) OR (“jaws”[All Fields])) AND ((((((((((((((((((“sinus floor augmentation”[MeSH Terms]) OR (“bone transplantation”[MeSH Terms])) OR (“sinus floor augmentation/adverse effects”[MeSH Terms])) OR (“sinus floor augmentation”[All Fields])) OR (“bone transplantation”[All Fields])) OR (“sinus floor augmentations”[All Fields])) OR (“maxillary sinus floor augmentation”[All Fields])) OR (“sinus augmentation therapy”[All Fields])) OR (“bone grafting”[All Fields])) OR (“sinus augmentation”[All Fields])) OR (“sinus augmentations”[All Fields])) OR (“sinus lift”[All Fields])) OR (“sinus lift augmentation”[All Fields])) OR (“sinus elevation”[All Fields])) OR (“sinus elevation procedure”[All Fields])) OR (“maxillary sinus floor elevation”[All Fields])) OR (“bone graftings”[All Fields])) OR (“bone transplantations”[All Fields])) OR (“augment bone graft”[All Fields]))) AND ((((((((((((((((“sinusitis”[MeSH Terms]) OR (“maxillary sinusitis”[MeSH Terms])) OR (“paranasal sinus diseases”[MeSH Terms])) OR (“postoperative complications”[MeSH Terms])) OR (“sinusitis”[All Fields])) OR (“maxillary sinusitis”[All Fields])) OR (“paranasal sinus diseases”[All Fields])) OR (“postoperative complications”[All Fields])) OR (“sinus infection”[All Fields])) OR (“sinusitides”[All Fields])) OR (“maxillary sinusitides”[All Fields])) OR (“paranasal sinus disease”[All Fields])) OR (“postoperative complication”[All Fields])) OR (“sinus augmentation complications”[All Fields])) OR (“sinus infections”[All Fields])) OR (“rhinosinusitis”[All Fields])) OR (“rhinosinusitides”[All Fields]))) AND (“surgery”[All Fields])
EMBASE	(‘bone atrophy’/exp OR ‘bone resorption’ OR ‘tooth implant’/exp OR ‘tooth implantation’/exp OR ‘dental implant’ OR (‘dental prosthesis’/exp AND ‘implant’/exp) OR ‘surgical dental treatment’) AND (‘sinus floor augmentation’/exp OR ‘bone graft’/exp OR ‘sinus lift’ OR ‘sinus elevation’ OR ‘sinus augmentation’) AND (‘postoperative complication’/exp OR ‘sinusitis’/exp OR ‘rhinosinusitis’/exp OR ‘sinus infection’ OR ‘maxilla sinusitis’/exp)
Scielo	((Sinus Floor Augmentation) OR (sinus lift) OR (Elevación del piso del seno maxilar) OR (elevación del seno) OR (levantamento de seio) OR (Sinus

	elevation)) AND ((sinusitis) OR (sinusite) OR (sinus infection) OR (infecção do sinus) OR (Rhinosinusitis) OR (sinusitis maxilar))
BVS	(tw:((mh:(“atrophy”)) OR (mh:(“atrofia”)) OR (mh:(“maxilla”)) OR (mh:(“maxilar”)) OR (mh:(“101inusit”)) OR (tw:(“maxilar edentulo”)) OR (tw:(“implante”)) OR (tw:(“101inusit edentula”)) OR (tw:(“101inusit edentada”)) OR (tw:(“maxilar desdentado”)) OR (tw:(“jaw”)))) AND (tw:((tw:(“sinus”)) OR (tw:(“seno”)) OR (tw:(levantamento de seio)) OR (tw:(enxerto ósseo)) OR (tw:(bone transplantation)) OR (tw:(elevación del seno)) OR (tw:(trasplante ósseo)))) AND (tw:((mh:(“sinusitis”)) OR (mh:(“sinusite”)) OR (tw:(maxillary sinusitis)) OR (tw:(sinusitis maxilar)) OR (tw:(sinusite maxilar)) OR (tw:(sinus infection)) OR (tw:(Infecção do seio)) OR (tw:(Rhinosinusitis))))
Cochrane	“sinus lift” in All Text OR “sinus elevation” in All Text OR “sinus augmentation” in All Text OR “Sinus Floor Augmentation” in All Text AND “Postoperative complications” in All Text OR Sinusitis in All Text OR “Maxillary sinusitis” in All Text OR “sinus infection” in All Text OR “rhinosinusitis” in All Text
Zygomatic	
Database	*Search terms*
Pubmed/Medline	((((((((((((((((((((((((“atrophy”[MeSH Terms]) OR (“bone resorption”[MeSH Terms])) OR (“dental implants”[MeSH Terms])) OR (“dental implantation”[MeSH Terms])) OR (“dental prosthesis”[MeSH Terms])) OR (“maxilla”[MeSH Terms])) OR (“jaw, edentulous”[MeSH Terms])) OR (“jaw”[MeSH Terms])) OR (“atrophy/surgery”[MeSH Terms])) OR (“bone resorption/physiopathology”[MeSH Terms])) OR (“maxilla/surgery”[MeSH Terms])) OR (“jaw, edentulous/rehabilitation”[MeSH Terms])) OR (“atrophies”[All Fields])) OR (“bone resorptions”[All Fields])) OR (“dental implant”[All Fields])) OR (“surgical dental prosthesis”[All Fields])) OR (“dental prosthesis implantation”[All Fields])) OR (“surgical dental treatment”[All Fields])) OR (“maxillary bone”[All Fields])) OR (“maxillae”[All Fields])) OR (“edentulous jaw”[All Fields])) OR (“edentulous jaws”[All Fields])) OR (“jaws”[All Fields])) AND (((((((((“zygoma”[MeSH Terms]) OR (“zygoma/surgery”[MeSH Terms])) OR (“zygomas”[All Fields])) OR (“malar bone”[All Fields])) OR (“cheek bones”[All Fields])) OR (“zygomatic arch”[All Fields])) OR (“malar”[All Fields])) OR (“zygomatic”[All Fields])) OR (“zygomatic implants”[All Fields]))) AND ((((((((((“sinusitis”[MeSH Terms]) OR (“maxillary sinusitis”[MeSH Terms])) OR (“paranasal sinus diseases”[MeSH Terms])) OR (“postoperative complications”[MeSH Terms])) OR (“sinus infection”[All Fields])) OR (“sinusitides”[All Fields])) OR (“maxillary sinusitides”[All Fields])) OR (“paranasal sinus disease”[All Fields])) OR (“postoperative complication”[All Fields])) OR (“sinus infections”[All Fields])) OR (“rhinosinusitis”[All Fields])) OR (“rhinosinusitides”[All Fields]))
EMBASE	(‘bone atrophy’/exp OR ‘bone resorption’ OR ‘tooth implant’/exp OR ‘tooth implantation’/exp OR ‘dental implant’ OR (‘dental prosthesis’/exp AND ‘implant’/exp) OR ‘surgical dental treatment’) AND (zygoma OR ‘temporal bone’ OR ‘zygomatic’ OR ‘zygoma’/exp) AND (‘postoperative complication’/exp OR ‘sinusitis’/exp OR ‘rhinosinusitis’/exp OR ‘sinus infection’ OR ‘maxilla sinusitis’/exp)
Scielo	((zygomatic) OR (zygoma) OR (malar) OR (“zygomatic implants”) OR (“zygomatic arch”)) AND (((sinusitis) OR (sinusite) OR (sinus infection) OR (infecção

	do sinus) OR (Rhinosinusitis) OR (sinusitis maxilar)))
BVS	((tw:((mh:(“atrophy”)) OR (mh:(“atrofia”)) OR (mh:(“maxilla”)) OR (mh:(“maxilar”)) OR (mh:(“102inusit”)) OR (tw:(“maxilar edentulo”)) OR (tw:(“implante”)) OR (tw:(“102inusit edentula”)) OR (tw:(“102inusit edentada”)) OR (tw:(“maxilar desdentado”)) OR (tw:(“jaw”))))) AND ((mh:(zigoma)) OR (mh:(zygoma)) OR (mh:(cigoma)) OR (zygomatic) OR (“implante zigomático”)) AND ((tw:((mh:(“sinusitis”)) OR (mh:(“sinusite”)) OR (tw:(maxillary sinusitis)) OR (tw:(sinusitis maxilar)) OR (tw:(sinusite maxilar)) OR (tw:(sinus infection)) OR (tw:(Infecção do seio)) OR (tw:(Rhinosinusitis)))))
Cochrane	“zygomatic” in All Text OR “zygoma” in All Text OR “zygomatic arch” in All Text OR “zygomatic implant” in Title Abstract Keyword in All Text AND “Postoperative complications” in All Text OR Sinusitis in All Text OR “Maxillary sinusitis” in All Text OR “sinus infection” in All Text OR “rhinosinusitis" in All Text in All Text

Table 2 - Inclusion and exclusion criteria applied in study selection

Sinus lift	
Inclusion criteria	*Exclusion criteria*
Studies with humans.	Studies with animals.
Patients with compromised bone height.	In vitro assays.
Studies that evaluated the occurrence of sinusitis after the maxillary sinus elevation procedure.	Case reports, case series, systematic reviews, and meta-analysis.
Prospective cohort, retrospective cohort, ambidirectional, or randomized controlled trial studies.	Publications in languages other than English, Portuguese and Spanish.
Studies in English, Portuguese or Spanish.	Studies that did not specify the surgery technique used.
Studies with patients without proven sinusitis or who were treated by an ENT* before surgery.	Studies that did not analyze the sinusitis occurrence based in the patient number.
Zygomatic	
Inclusion criteria	*Exclusion criteria*
Studies with humans	Studies with animals
Patients with atrophic maxilla	In vitro assays
Studies that evaluated the occurrence of sinusitis after the zygomatic implant surgery	Case reports, case series, systematic reviews, and meta-analysis
Prospective cohort, retrospective cohort, ambidirectional, or randomized controlled trial studies	Publications in languages other than English, Portuguese and Spanish
Studies in English, Portuguese or Spanish	Studies that did not specify the surgery technique used.
Studies with patients without proven sinusitis or who were treated by an ENT* before surgery	Studies that did not analyze the sinusitis occurrence based in the patient number.

*ENT = ear, nose and throat doctor

Table 3 - Characteristics of sinus lift studies included in the quantitative analysis (18 studies)

Author (year)	Sample size (patients)	Sinus lifted	Sinus lift technique	Trans- and postoperative complications	Occurrence of sinusitis	Implant survival	Follow-up time
Alayan and Ivanovski 2018	60	60	Lateral window technique	Maxillary sinusitis, sinus membrane perforation, wound dehiscence, bleeding, facial edema and hematose	1	Not informed	At least 6 months
Beaumont et al. 2005	45	59	Lateral window technique	Maxillary sinusitis, sinus membrane perforation and infection	1	Not informed	Not informed
Borges et al. 2011	15	30	Lateral window technique	Maxillary sinusitis, sinus membrane perforation, implant failure, infection, membrane exposure, and sinuses with an incomplete closing of the lateral window	1	Test group: 96.4% Control group: 100%	6 months
Guerrero 2015	68	101	Lateral window technique	Maxillary sinusitis, sinus membrane perforation, implant failure, wound dehiscence, bleeding and infection	3	89%	Between 24 and 132 months
Kasabah et al. 2003	118	146	Lateral window technique	Sinus membrane perforation	0	Not informed	Not informed
Khoury, Keller, and Keeve 2017	118	198	Lateral window technique	Sinus membrane perforation and implant failure	0	99.50%	Up to 10 years
E. S. Kim et al. 2016	30	At least 30	Lateral window technique	No complication	0	100%	2 years
Lambert, Lecloux, and Rompen 2010	40	50	Lateral window technique	Sinus membrane perforation, implant failure, bleeding caused by a subantral artery lesion	0	98%	3.7 years
W. B. Park et al. 2019	63	65	Lateral window technique	Sinus membrane perforation, wound dehiscence, bleeding, facial edema, hematoma, graft failure, leakage of cystic fluid or purulent exudate from sinus pathoses, incision line opening and nasal bleeding	0	100%	Mean of 11.5 months
W.-B. Park, Han, and Kang 2021	38	At least 38	Lateral window technique	Maxillary sinusistis, sinus membrane perforation and implant failure	3	89.47%	Mean of 12.62 years (5.8 to 22 years)
G. M. Raghoebar et al. 1999	75	140	Lateral window technique	Maxillary sinusitis, sinus membrane perforation, implant failure, wound dehiscence, hematoma, and seroma	3	93.31%	Mean of 32 months (12 to 84 months)
Sakkas et al. 2016	99	105	Lateral window	Maxillary sinusitis, sinus membrane perforation, wound	2	100%	Up to 1

			technique	dehiscence and abscess			year
Timmenga et al. 1997	45	85	Lateral window technique	Maxillary sinusitis and sinus membrane perforation	2	Not informed	12 to 60 month
Wannfors et al. 2000	40	At least 40	Lateral window technique	Maxillary sinusitis, sinus membrane perforation and implant failure	2	89.58%	1 year
Zijderveld et al. 2008	100	118	Lateral window technique	Maxillary sinusitis, sinus membrane perforation, implant failure, wound dehiscence, infection and graft loss	1	98.35%	Not informed
Chen et al. 2017	37	At least 37	Transcrestal technique	No complication	0	100%	1 year
Kher et al. 2014	21	At least 21	Transcrestal technique	Wound dehiscence and edema	0	100%	At least 1 year
Engelke et al. 2003	83	118	SALSA technique	Maxillary sinusitis, sinus membrane perforation, and implant failure	1	94.75%	Up to 5 years
Total	1095	At least 1441	-	-	20	89-100%	6 months – 22 years

Table 4 - Characteristics of zygomatic studies included in the quantitative analysis (9 studies)

Author (year)	Sample size (patients)	Zygomatic technique	Bone graft	Trans- and postoperative complications	Occurrence of sinusitis	Implant survival	Follow-up time
Davo, Malevez, and Rojas 2007	18	Intrasinus	Not Informed	Maxillary inusitis and discomfort	1	100%	14 months
Davó et al. 2008	42	Intrasinus	Not Informed	Maxillary sinusitis, pain, fistula, oroantral communication and edema	1	100%	20.5 months
Davó 2009	24	Intrasinus	Yes	Maxillary sinusitis, implant failure and pain	5	97.4%	5 years
Hinze et al. 2013	10	Intrasinus	Yes	Implant failure, pain, and hematoma	0	90.9%	6 months
Stiévenart and Malevez 2010	20	Intrasinus	Yes	Maxillary sinusitis, implant failure, tissue inflammation definitive and cheekbone hypoaesthesia	1	96%	40 months
Borgonovo et al. 2021	23	Extrasinus	No	Sinus membrane perforation and peri-implant mucositis	0	100%	1 year
Goker, Grecchi, Grecchi, et al. 2020	92	Extrasinus	No	Maxillary sinusitis, implant failure, fistula, oroantral communications, abscess, infection, fracture of the zygomatic bone, permanent paresthesia and temporary neurosensory deficits	0	98.08%	Mean of 34.5 months (6 to 72 months)
Atalay et al. 2017	16	Intrasinus and extrasinus	Not Informed	Implant failure and perimucositis.	0	93.7%	28 months
R. T. E. Araújo et al. 2017	37	Sinus slot technique	Not Informed	Maxillary sinusitis, implant failure, pain, oroantral communication, hematoma, infection paresthesia of the infraorbital nerve and wound dehiscence.	8	98.44%	At least 12 months
Total	282	-	-	-	16	90.9-100%	6 months – 72 months

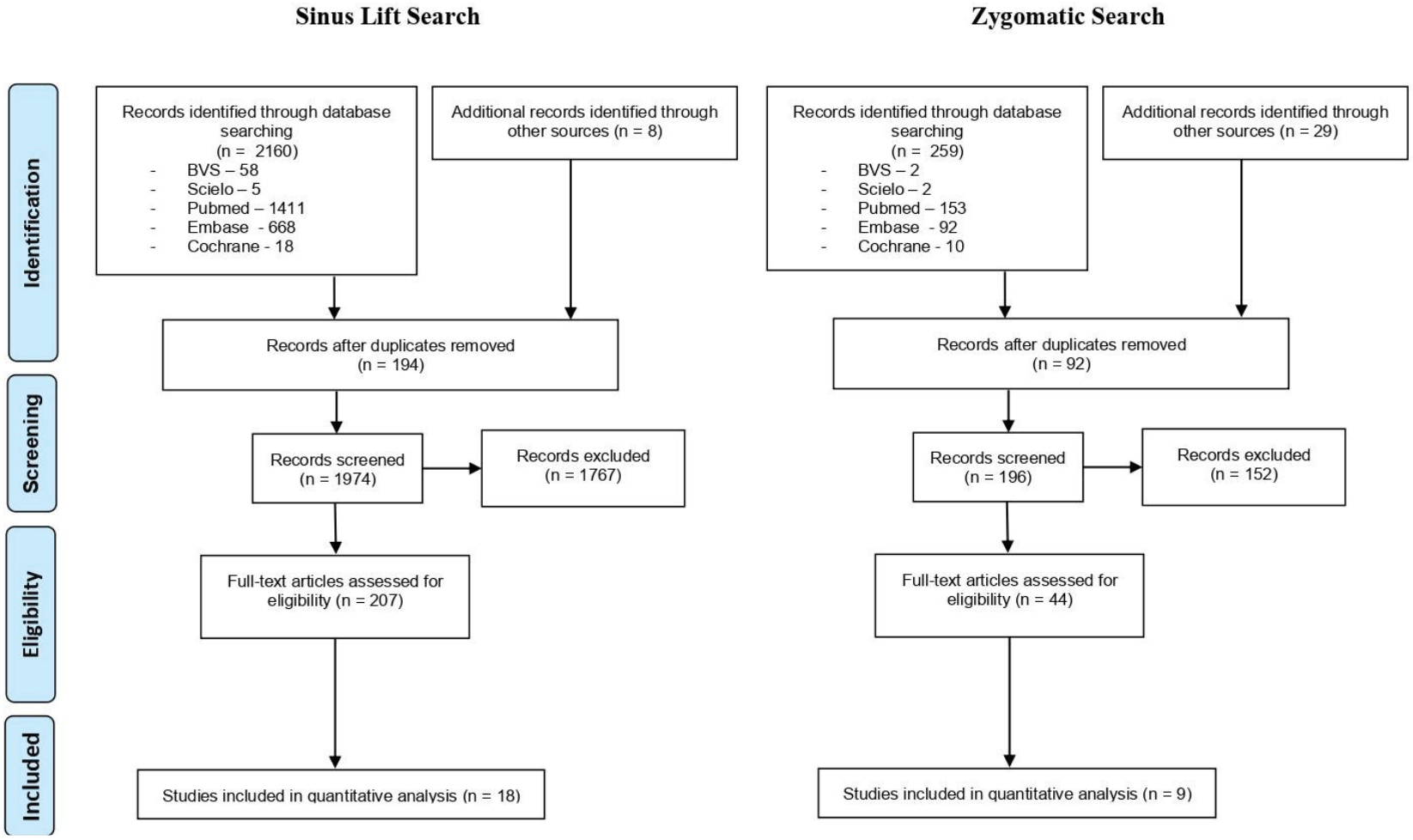

Figure 1 - PRISMA flow diagram.

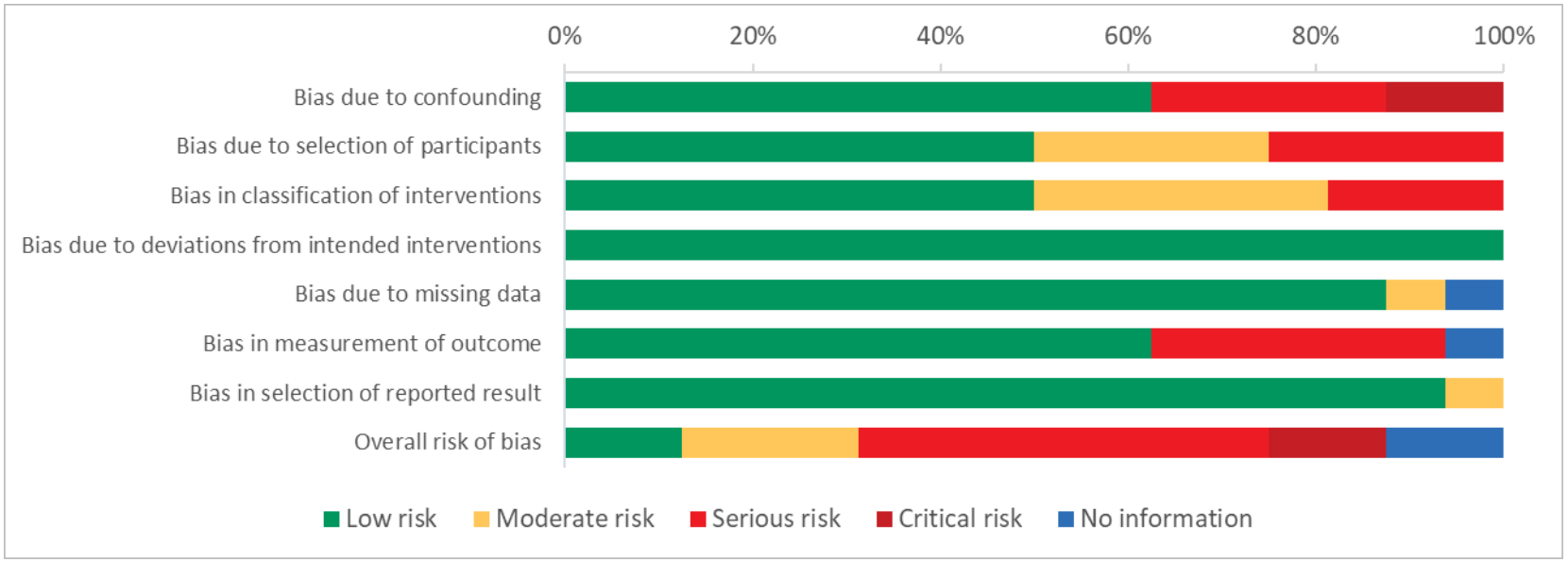

Figure 2 – Risk of bias of sinus lift observational studies

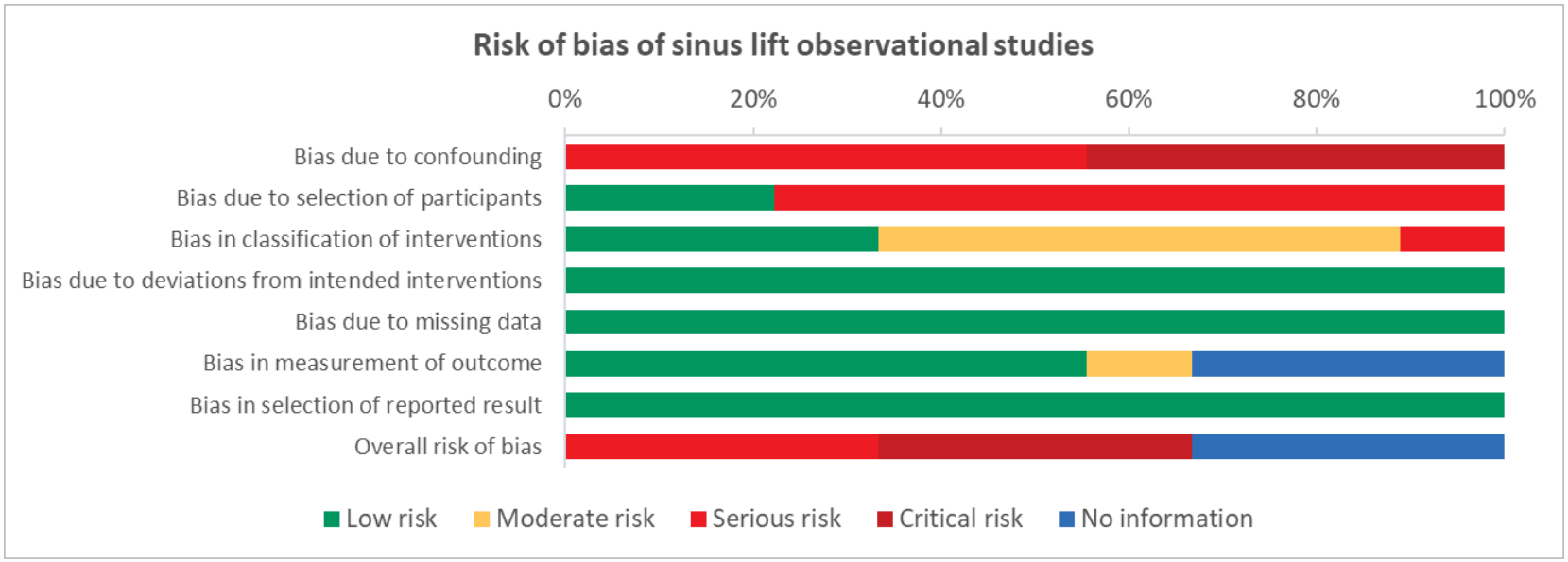

Figure 3 - Risk of bias of zygomatic observational studies

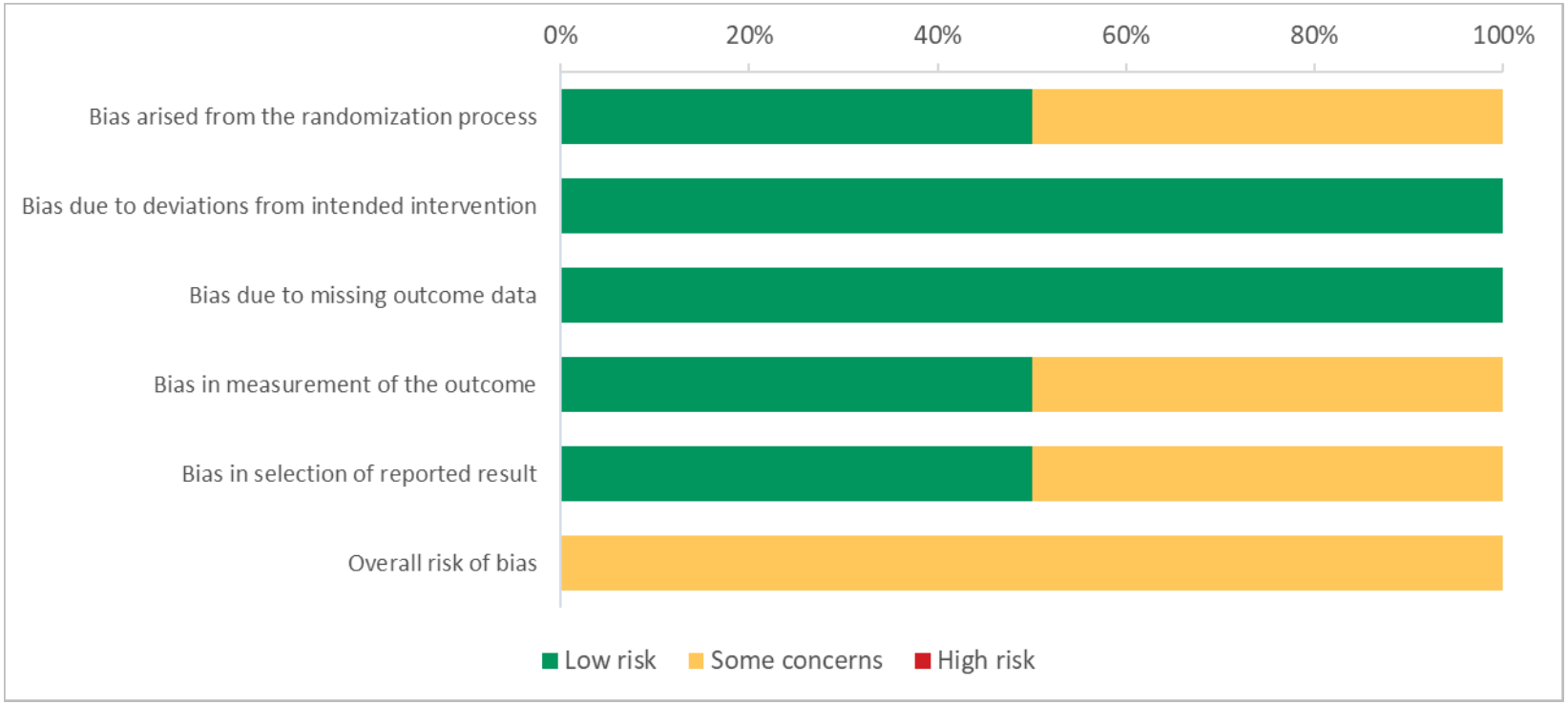

Figure 4 – Risk of bias of sinus lift randomized clinical trial

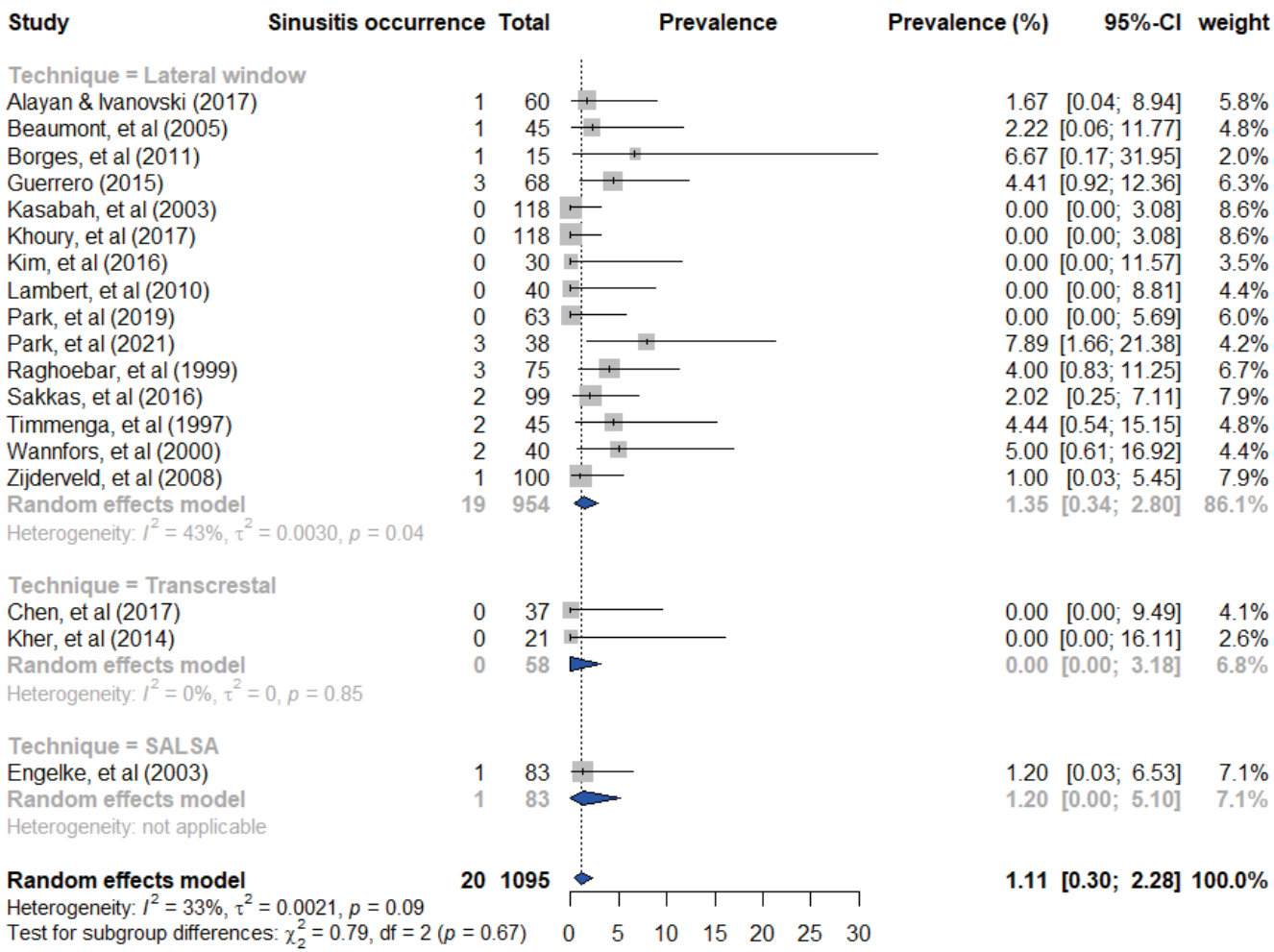

Figure 5 - Forest plot comparison of sinusitis after different sinus lift techniques from 15 studies with lateral window technique, 2 studies with transcrestal technique, 1 study with SALSA technique.

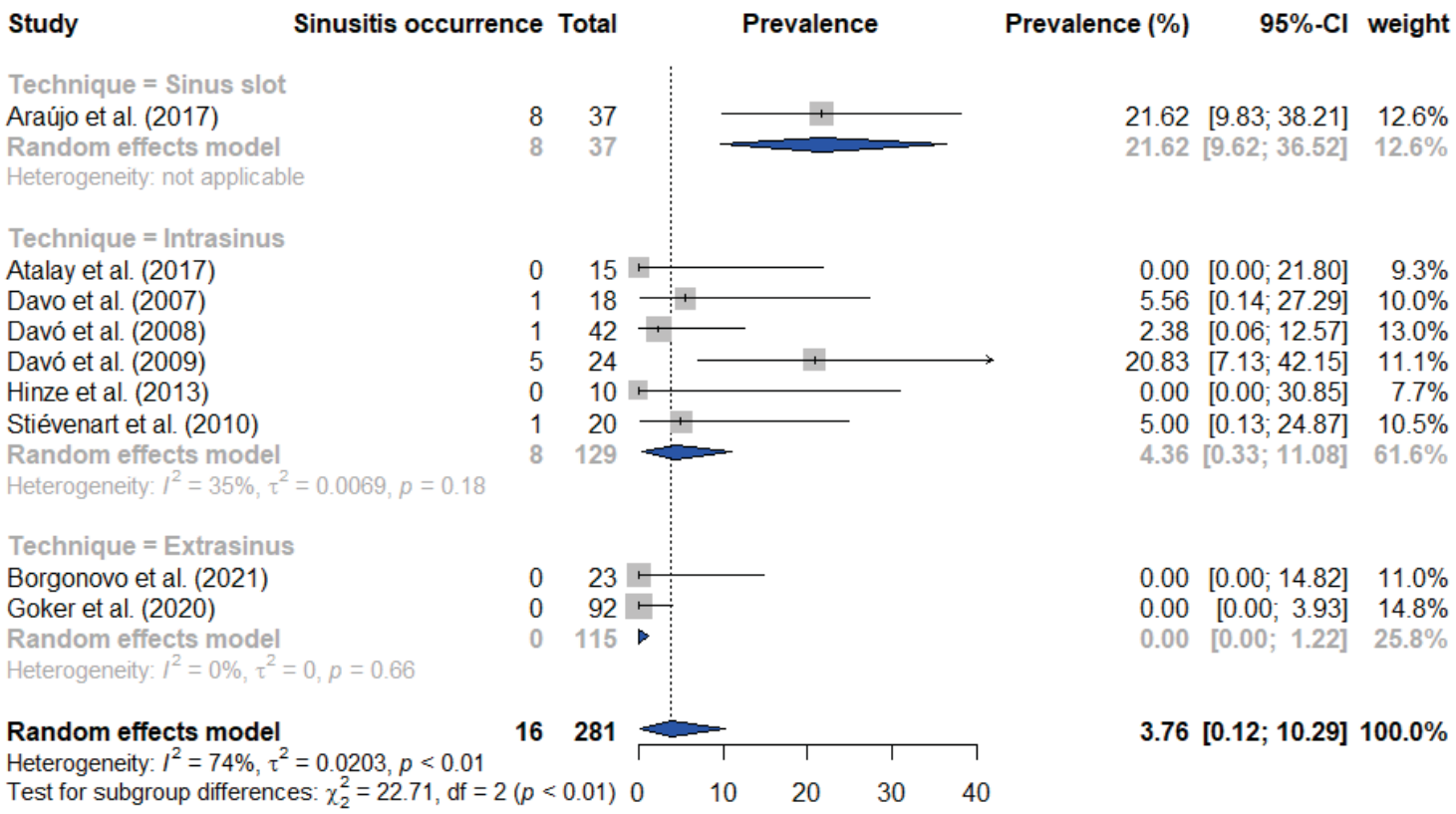

Figure 6 - Forest plot comparison of sinusitis after different zygomatic implant surgery techniques from 1 study with sinus slot technique, 6 studies with intrasinus technique, 2 studies with extrasinus technique.

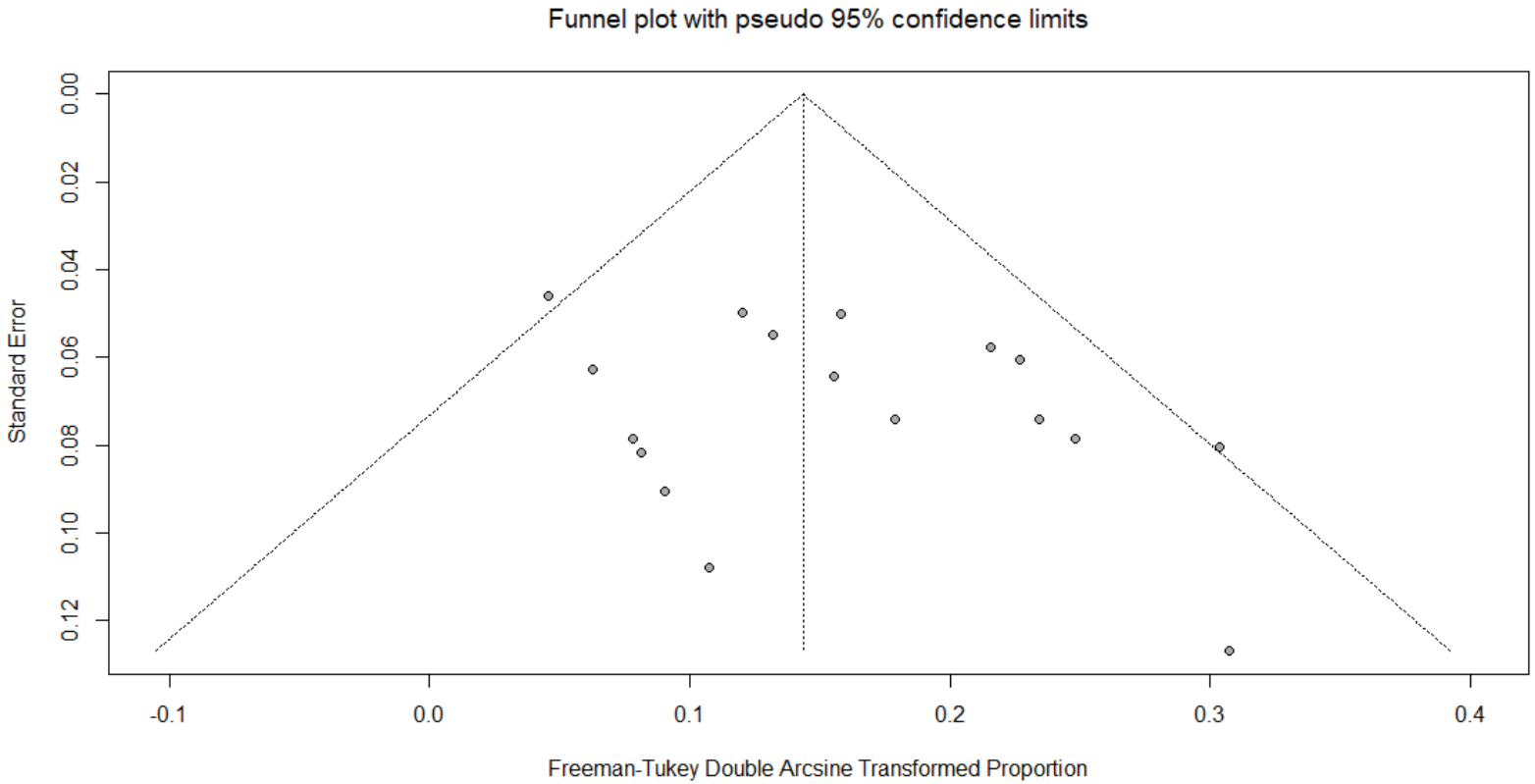

Figure 7 - Funnel plot measuring the odds ratio of occurrence of sinusitis after sinus lift procedure.

5 DISCUSSÃO

Conhecer os fatores que podem influenciar na falha de osseointegração e ocorrência de sinusite é de extrema importância para que o clínico possa entender as pré-disposições do paciente, orientar e, muitas das vezes, guiar a escolha do melhor tratamento para este paciente.

Vários fatores exógenos relacionados aos implantes, como o desenho do implante, comprimento, diâmetro, presença de tratamento de superfície, topografia da superfície, molhabilidade, existência de revestimento bioativo, entre outros bem como as habilidades do cirurgião podem influenciar na osseointegração (LEE; BANCE, 2019). Entretanto, a influência dos fatores endógenos no processo ainda não foi totalmente elucidada.

Já se sabe que características biológicas do paciente como idade, doenças sistêmicas descontroladas, determinadas medicações e radioterapia local prévia podem representar um fator de risco a osseointegração (LEE; BANCE, 2019). Entretanto, alguns indivíduos que não apresentam fatores de riscos conhecidos, e são adequadamente preparados para o procedimento cirúrgico ainda estão sujeitos a falhas na osseointegração e/ou complicações pós-operatorias.

Fatores intrínsecos ao indivíduo, como os polimorfismos genéticos demostram ter um papel importante no sucesso dos tratamentos com implantes tanto ortopédicos como dentários, já que a osseointegração é semelhante em ambos.

Os resultados aqui reportados por metanálise traz luz a influência dos SNPs em MMPs na perda de implantes osseointegrados. Polimorfismos em diferentes genes já foram associados a diversas patologias, sendo que alelos polimórficos podem representar um risco aumentado de desenvolver a patologia, como cancer (SHAMOUN et al., 2021), doenças cardiovasculares (LI; WANG; ZHANG, 2021), e lúpus eritematoso sistêmico (YANG et al., 2022), por outro lado, alelos polimórficos podem representar fator de proteção como na depressão, hepatite e câncer (FENG et al., 2015; HONG et al., 2022; XUE et al., 2022). Padrões semelhantes também foram observados no nosso estudo, já que alguns alelos foram associados a um aumento do risco de falha de osseointegração (MMP-8 g.-799 C>T e MMP-1 g. 3' UTR C>T na população caucasiana) e outros foram fatores protetivos (MMP-1 g.-1607 G>GG e MMP-1 g. 3' UTR C>T na população asiática).

Apesar da metanálise de avaliação de SNP em MMPs trazer resultados importantes, ainda são encontrados poucos estudos na literatura. Portanto, é imprescindível que invesigações em diferentes SNPs de MMPs sejam conduzidos para ampliar o conhecimento da influência das MMPs no processo de osseointegração, inclusive em diferentes populações, uma vez que a origem étnica pode influenciar as frequências alélicas (MOURANT et al., 1976). Dessa forma, marcadores genéticos para suscetibilidade à perda de implantes poderão ser identificados, contribuindo na busca de estratégias para garantir um tratamento com implante mais assertivo e individualizado.

Complicações pós-operatorias são esperadas após a instalação de implantes. Na odontologia, quando se olha especialmente para implantes zigomáticos ou mesmo implantes convencionais associados à técnica de levantamento de seio, a ocorrência de sinusite desponta como uma complicação frequente.

Hsu e colaboradores (2022) recentemente evidenciou que o levantamento de seio pela técnica transcrestal tem menor incidência de perfuração da membrana sinusal e ocorrência de sinusite, o que corrobora a metanálise realizada. Nosso estudo mostrou que a taxa de sinusite após implante zigomático com técnica intra-sinusal é de 3,76%, e após levantamento do seio é de 1,11%. A ocorrência de sinusite é dependente da invasividade da técnica utilizada.

Ainda, sugerimos que sejam realizados mais estudos clínicos onde o parâmetro principal seja a avaliação de sinusite e estudos randomizados comparando diretamente a taxa de sinusite entre o procedimento de instalação de implantes zigomáticos e levantamento de seio. Isso irá ampliar o conhecimento e garantir o aperfeiçoamento de técnica, seleção e análise dos casos para diminuir a incidência da sinusite pós-operatoria e ainda melhor conduta nos casos dessa complicação.

Um ponto importante na metanálise é avaliar estudo com metodologia e desenho restrito. Os estudos reportados aqui seguiram rígidos critérios de seleção e os vieses foram discutidos. Apesar das limitações, o estudo contribuiu para uma melhor compreensão das complicações durante e após a osseointegração.

6 CONCLUSÃO

Com relação à associação de polimorfismos de metaloproteases e falha de osseointegração, conclui-se que o polimorfismo MMP-1 g.-1607 G>GG (rs1799750) foi estatisticamente associado à falha na osseointegração como fator protetor. O MMP-8 g.-799 C>T (rs11225395) está associado a um maior risco de falha na osseointegração do implante. O MMP-1 g. 3' UTR C>T (rs5854) está associado a um maior risco de falha do implante na população caucasiana, enquanto na população asiática é um fator protetor. Por fim, a MMP-3 g.-1612 5A>6A (rs3025058) e a MMP-1 g.-519 A>G (rs1144393) parecem não apresentar associação com falha na osseointegração.

Já a metanálise de ocorrência de sinusite demonstrou que a prevalência combinada de sinusite após a instalação do implante zigomático foi de 3,76%, e após o procedimento de levamento de seio foi de 1,11%. Na análise de subgrupo, a maior prevalência de sinusite para instalação de implantes zigomático foi a técnica de slot (21,62%) e para o levantamento de seio a abordagem da janela lateral (1,35%).

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ANEXO 1 – COMPROVANTES DE ENVIO E ACEITE DOS ARTIGOS PELA REVISTA

From: Oral and Maxillofacial Surgery
To: Roberta Rocha
Subject: Oral and Maxillofacial Surgery: Decision on your manuscript
Date: sábado, 13 de maio de 2023 06:37:35

Ref: Submission ID 3e5c8bb4-57e9-4f2c-b16a-a5142afae73d

Dear Dr Schroder Rocha,

Re: "Comparison of sinusitis rate after sinus lift procedure and zygomatic implant surgery: a meta-analysis."

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Once again, thank you for choosing Oral and Maxillofacial Surgery, and we look forward to publishing your article.

Kind regards,

Henning Schliephake
Editor
Oral and Maxillofacial Surgery

From: Roberta Schroder Rocha
To: Roberta Rocha
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Sent: Tuesday, May 16, 2023 11:36:43 PM
To: Roberta Schroder Rocha <roschroder@hotmail.com>
Subject: [bjos] Submission Acknowledgement

Dear authors., Roberta Schroder Rocha:

Thank you for submitting the manuscript, "Is polymorphism in metalloproteinases a risk factor for implant osseointegration failure? a systematic review and meta-analysis" to Brazilian Journal of Oral Sciences. With the online journal management system that we are using, you will be able to track its progress through the editorial process by logging in to the journal web site:

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If you have any questions, please contact me. Thank you for considering this journal as a venue for your work.

Altair Antoninha Del Bel Cury

Editor-in-chief

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ANEXO 2 – OUTROS ARTIGOS PUBLICADOS DURANTE O DOUTORADO RELACIONADOS AO TEMA

Original Article
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Influence of risk factors on the long-term survival of oral rehabilitation with extra-narrow implants: a retrospective study

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Larissa Carvalho TROJAN[4]

Abstract

Objective: This study aimed to retrospectively collect clinical data to evaluate the influence of possible risk factors on the long-term success of implant treatment with extra-narrow (2.9 mm diameter) implants in a daily dental practice setting. Methodology: Data were collected from records of patients who received at least one extra-narrow implant from 2012 to 2017, regarding implant survival, prosthesis survival, patient characteristics, and implant characteristics. The association between the dependent variables "implant survival", "prosthesis survival," and "adverse events" related to patient and implant characteristics was statistically evaluated by chi-square tests. Moreover, implant and prosthesis survival were analyzed by Kaplan-Meier survival curves. Results: The sample was constituted of 58 patients (37 women and 21 men) with a mean age of 54.8 years old (SD: 12.5), followed up for up to eight years. In total, 86 extra-narrow implants were placed within this sample. Four implants were lost, resulting in an implant survival rate of 95.3%. A total of 55 prostheses were inserted and only one (1.8%) was lost, resulting in a prosthesis survival rate of 98.2%. The mean implant and prosthesis survival time was, respectively, 7.1 years and 6.3 years, according to the Kaplan-Meier survival analysis. A correlation was found between smoking and implant loss, which makes implant loss eight times more likely to occur in smokers than non-smokers. A significant association was also found between prosthesis loss and previous need of prosthesis repair. However, it was not considered clinically relevant. No association was found between the occurrence of adverse events and later implant or prosthesis loss. Conclusion: High implant and prosthesis survival rates were found in the long term for treatment with extra-narrow implants. Moreover, a significant correlation between smoking and implant loss was observed.

Keywords: Prostheses and implants. Survival rate. Risk factors. Smokers.

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Introduction

Dental implants are widely used with great success and long-term survival rates in completely and partially edentulous patients.[1,2] The implant diameter choice is based on several factors and, since an adequate bone volume and interdental space are required to produce good results, single-tooth rehabilitation in the anterior region can be challenging.[3] Moreover, when placed in the atrophic alveolar bone, standard-diameter implants can expose their threads and lead to failure.[4] This is common in cases of agenesis, present in 2.2% to 7.6% of the population,[5] and after tooth extraction, in which the alveolar bone resorption is progressive.[4] Other conditions, such as trauma, neoplasia, and denture wearing, are related to reduced space.[6]

Some treatment approaches are suggested to successfully manage patients with limited space for standard dental implants, such as bone augmentation techniques. However, these approaches are more invasive, presenting higher risks of complications, besides a longer time and additional costs.[7] In cases of limited mesiodistal space, orthodontic treatment and adhesive partial denture are suggested, but it might not meet all patients' expectations. Thus, narrow-diameter implants emerge as a reliable alternative.

Although there is no consensus in the literature on the definition of narrow implants, in general, implants with a diameter narrower than 3.5 mm are considered narrow whereas implants with diameters narrower than 3.0 mm are described as extra-narrow or mini implants.[8] Reduced bleeding, postoperative discomfort, and healing time are some of the reported advantages of these implants when compared with grafting procedures.[4] Moreover, narrow and extra-narrow implant survival rates from 80% to 100% were reported in a follow-up period of up to seven years.[5,6,9,10]

Regarding aesthetic aspects, which are especially important in the rehabilitation in the anterior region, good results seem to be produced by narrow implants.[11] The reduced diameter makes it possible to achieve an adequate 3-dimensional position, respecting the necessary distance between implant and adjacent teeth, as well as surrounding bone, to facilitate papillae formation and its maintenance in the long term.[9] This is especially important to achieve good aesthetic outcomes in upper and lower lateral incisors and central incisors, which present the smallest mesiodistal dimensions.[12] However, possible mechanical complications and other risk factors must be considered since the reduced bone–implant contact may lead to implant fractures.[3]

Therefore, this study aimed to retrospectively collect clinical data to evaluate the influence of possible risk factors on the long-term survival of oral rehabilitation with extra-narrow (2.9 mm diameter) implants, in a daily dental practice setting.

Methodology

Sample and study parameters

This study was reviewed and approved by the local Research Ethics Committee (Araraquara, Brazil; approval no. 3.553.077). Inclusion criteria were patients who had at least one 2.9-mm-diameter implant (Facility, Neodent, Curitiba, Brazil), inserted at ILAPEO College (Curitiba, Brazil) from 2012 to 2017, whose records presented postoperative clinical follow-up data.

Data was retrospectively collected from the patients' records, according to the following parameters:

Implant survival: implant survival was defined as no implant loss at each follow-up visit.

Prosthesis survival: prosthesis survival was defined as the prosthesis remaining *in situ* at each follow-up visit.

Risk factors: patient demographic and general health data; general data for implants and prosthesis abutments, type of loading, and adverse events occurred after surgery.

Statistical analysis

All analyses were performed using SPSS 16.0 for Windows (SPSS Inc. Headquarters, Chicago, USA). Descriptive summary statistics were estimated for all parameters. Quantitative parameters were described by mean, standard deviation, median, quartiles, minimum, and maximum. For qualitative variables, frequencies were given. Survival rates were estimated by dividing the number of events by the total number of implants/prostheses evaluated.

The association between the dependent variables "implant survival," "prosthesis survival," and "adverse events" and patient and implant characteristics was evaluated by chi-square tests and by estimating the relative frequencies, odds ratios (OR), and 95%

confidence intervals. Missing data concerning a specific parameter was not included in association analyses. It was not possible to estimate the odds ratio of several variables since there was not sufficient sample to perform the test.

Implant and prosthesis survival were further analyzed by Kaplan-Meier survival curves. Some factors could not be analyzed by Kaplan-Meier survival curves due to insufficient sample. The significance level for all tests was oblique $p<0.05$.

Results

All patients rehabilitated with at least one extra-narrow implant from 2012 to 2017 at ILAPEO College were included. The sample was constituted of 58 patients, of which 37 (63.8%) were women and 21 (36.2%) men, with a mean age of 54.8 years old (SD: 2.5; range: from 23.7 to 83.9). A total of 86 extra-narrow (2.9 mm diameter) implants were placed. Their length ranged from 10 to 14 mm, to support single or multi-unit fixed and removable prostheses in maxilla and mandible. Patients were followed up for a mean period of 2.8 years (SD: 1.9; up to 8.0). Four implants were lost due to lack of osseointegration, resulting in an implant survival rate of 95.3%. Three of these losses occurred before loading.

The most frequent patients' medical condition was psychological limitations (10;17.2%), followed by smoking habit (5; 8.6%), thyroid dysfunction (4; 6.9%), coagulation disorders (5.2%), bone metabolism disorders (3; 5.2%), severe bruxism (2; 3.4%), bisphosphonate therapy for more than one year (2; 3.4%), poor healing capacity (1; 1.7%), regular steroid use (1; 1.7%), and previous radiotherapy in the head/neck (1; 1.7%).

The correlation between patient-related variables and implant loss are shown in Table 1. A correlation was found between smoking and implant loss, which makes implant loss eight (95% CI 1.0–63.9) times more likely to occur in smokers than non-smokers ($p=0.024$).

Regarding implant-related variables, extra-narrow implants with 14 mm length were the most used ones (39; 45.3%). The most frequent insertion site was the lower central incisor (24; 27.9%), followed by the upper lateral incisor (19; 22.1%). Insertion torques

Table 1- Relative frequencies of patient-related variables and their association with implant loss

Implant loss?		Yes		No		Total	OR (95% CI)	p-value
		N	%	N	%	N		
Sex	Woman	4	6.6	57	93.4%	61	ł	0.246
	Man	0	0.0	25	100.0%	25	(ref.)	
Presence of thyroid dysfunction?	Yes	1	25.0	3	75.0%	4	8.8 (0.7–111.3)	0.176
	No	3	3.7	79	96.3%	82	(ref.)	
Presence of coagulation disorders?	Yes	0	0.0	3	100.0%	3	ł	0.894
	No	3	3.8	77	96.2%	80	(ref.)	
Presence of poor healing capacity?	Yes	0	0.0	1	100.0%	1	ł	0.964
	No	3	3.7	79	96.3%	82	(ref.)	
Regular steroid use?	Yes	0	0.0	1	100.0%	1	ł	0.953
	No	4	4.8	80	95.2%	84	(ref.)	
Previous radiotherapy in the head/neck?	Yes	0	0.0	1	100.0%	1	ł	0.953
	No	4	4.8	80	95.2%	84	(ref.)	
Bisphosphonate therapy?	Yes	0	0.0	3	100.0%	3	ł	0.864
	No	4	4.9	78	95.1%	82	(ref.)	
Psychological limitations?	Yes	0	0.0	17	100.0%	17	ł	0.402
	No	4	5.9	64	94.1%	68	(ref.)	
Presence of bone metabolism disorders?	Yes	0	0.0	4	100.0%	4	ł	0.822
	No	4	4.9	77	95.1%	81	(ref.)	
Smoking?	Yes	2	18.2	9	81.8%	11	8.0 (1.0–63.9)	0.024*
	No	2	2.7	72	97.3%	74	(ref.)	

*Statistically significant at $p<0.05$.
ł No sufficient sample size to calculate.

Table 2- Relative frequencies of implant-related variables and their association with implant loss

Implant loss?		Yes		No		Total	OR (95% CI)	p-value
		N	%	N	%	N		
Implant length	10 mm	0	0.0%	17	100.0%	17	ł	
	12 mm	3	7.7%	36	92.3%	39	2.5 (0.2–22.8)	0.857
	14 mm	1	3.6%	27	96.4%	28	(ref)	
Region of implant placement	Lower canines	0	0.0%	4	100.0%	4	ł	
	Lower central incisors	1	2.9%	34	97.1%	35	0.2 (0.0–3.2)	0.745
	Lower molars	0	0.0%	3	100.0%	3	ł	
	Lower premolars	0	0.0%	7	100.0%	7	ł	
	Upper canines	0	0.0%	1	100.0%	1	ł	
	Upper lateral incisors	2	10.5%	17	89.5%	19	0.7 (0.0–9.3)	0.794
	Upper premolars	1	14.3%	6	85.7%	7	(ref)	
	Others	0	0.0%	10	100.0%	10	ł	
Insertion torque (N.cm)	10–35	1	4.5%	21	95.5%	22	0.6 (0.0–5.8)	0.636
	36–60	3	7.7%	36	92.3%	39	(ref)	
Prosthesis type	Multi-unit fixed prosthesis	0	0.0%	42	100.0%	42	ł	ł
	Overdenture	0	0.0%	13	100.0%	13	ł	
	Single-unit prosthesis	1	4.0%	24	96.0%	25	(ref)	
Time until loading	Immediate loading	0	0.0%	40	100.0%	40	ł	
	1–4 months	1	33.3%	2	66.7%	3	0.5 (0.0–8.9)	0.638
	5–12 months	0	0.0%	26	100.0%	26	ł	
	> 12 months	0	0.0%	11	100.0%	11	ł	
	Not loaded	3	50.0%	3	50.0%	6	(ref)	
Final prosthesis retention	Cemented	0	0.0%	15	100.0%	15	ł	ł
	Overdenture	0	0.0%	12	100.0%	12	ł	
	Screwed	0	0.0%	19	100.0%	19	(ref)	
Peri-implant bone loss?	Yes, more than 1.5 mm	1	16.7%	5	83.3%	62	3.5 (0.3–40.6)	0.311
	No	3	5.4%	53	94.6%	56	(ref)	
Any prosthesis repair?	Yes	0	0.0%	2	100.0%	2	ł	ł
	No	0	0.0%	48	100.0%	48	(ref)	

*Statistically significant at p<0.05.

from 36 to 60 N.cm were reached in most implants (39;45.3%). A peri-implant bone loss greater than 1.5 mm was observed in six (7.0%) implants. No significant association was found between implant characteristics and implant loss (Table 2).

In total, 55 prostheses were inserted. Only one (1.8%) was lost, resulting in a prosthesis survival rate of 98.2%. Regarding the type of loading, 40 (46.5%) implants were immediately loaded whereas the other 40 were loaded after one month or more. Most implants were used in restorations supported by one extra-narrow implant (44; 51.2%). A total of 42 (48.8%) implants were used as support for multi-unit fixed prostheses, 25 (29.1%) for single-unit prostheses, and 13 (15.1%) for overdentures. For the other six implants, the prothesis type was not reported.

No correlation was found between patients' medical conditions and prosthesis loss (Table 3). However, a significant association was found between prosthesis loss and previous need of prosthesis repair (p=0.040; Table 4).

Regarding adverse events, four (4.7%) occurrences were reported: two (2.3%) chronic pain episodes and two (2.3%) local inflammatory reactions. No correlation was found between patient characteristics or implant-related variables and adverse events (Tables 5 and 6).

Figure 1 and Figure 2 show the implants and prostheses survival analysis by Kaplan-Meier survival curves. The mean implant and prosthesis survival time was, respectively, 7.1 years and 6.3 years (Table 7).

Table 3- Relative frequency of patient-related variables and their association with prosthesis loss

Prosthesis loss?		Yes		No		Total		p-value
		N	%	N	%	N	%	
Sex	Woman	0	0.0%	30	100.0%	30	100.0%	0.072
	Man	1	5.0%	19	95.0%	20	100.0%	
Presence of thyroid dysfunction?	Yes	0	0.0%	2	100.0%	2	100.0%	0.824
	No	1	2.1%	47	97.9%	48	100.0%	
Presence of coagulation disorders?	Yes	0	0.0%	2	100.0%	2	100.0%	0.861
	No	1	2.2%	45	97.8%	46	100.0%	
Presence of poor healing capacity?	Yes	0	0.0%	0	0.0%	0	0.0%	0.952
	No	1	2.1%	47	97.9%	48	100.0%	
Presence of incomplete jawbone growth?	Yes	0	0.0%	0	0.0%	0	0.0%	0.783
	No	1	2.0%	49	98.0%	50	100.0%	
Regular steroid use?	Yes	0	0.0%	0	0.0%	0	0.0%	0.953
	No	1	2.0%	48	98.0%	49	100.0%	
Previous radiotherapy in the head/neck?	Yes	0	0.0%	1	100.0%	1	100.0%	0.953
	No	1	2.1%	47	97.9%	48	100.0%	
Bisphosphonate therapy?	Yes	0	0.0%	1	100.0%	1	100.0%	0.864
	No	1	2.1%	47	97.9%	48	100.0%	
Psychological limitations?	Yes	0	0.0%	8	100.0%	8	100.0%	0.402
	No	1	2.4%	40	97.6%	41	100.0%	
Presence of bone metabolism disorders?	Yes	0	0.0%	2	100.0%	2	100.0%	0.822
	No	1	2.1%	46	97.9%	47	100.0%	
Smoking?	Yes	0	0.0%	3	100.0%	3	100.0%	0.568
	No	1	2.2%	45	97.8%	46	100.0%	

From variables that showed significance by the chi-square test, factors that could influence survival were evaluated. Thus, it was found that the mean implant survival time for non-smokers was greater than for smokers (3.7 years for smokers and 7.2 for non-smokers; p=0.002) (Figure 3 and Table 7). The mean implant and prosthesis loss time was, respectively, 1.7 years (SD: 1.9) and 0.9 years.

Discussion

Implant-supported prostheses proved to be a good choice for the treatment of totally or partially edentulous patients. In this study, high implant (95.3%) and prosthesis (98.2%) survival rates were found in a follow-up period of up to eight years, showing that extra-narrow implants are also a reliable option, especially to rehabilitate regions with limited space. Moreover, the treatment approach used in similar situations, in which conventional implants are inserted in grafted areas, has been reported to present lower survival rates (90% at five years of follow-up).[13] Besides the association between dental implant failure and previous augmentation techniques, several complications, such as graft exposure/loss and infections, have also been reported concerning this approach.[14]

The results obtained in this study are very similar to those obtained by other authors, presenting high long-term survival rates, ranging from 94.3%[15] to 96.8%[5] for extra-narrow implants. Moreover, while some authors state that a reduced-diameter implant could lead to lower survival rates when compared with standard-diameter implants, studies show that they do not differ greatly in both implant and prosthesis survival and success rates.[16,17]

It is important to identify potential risk factors associated with implant and prosthesis failure and evaluate if it is possible to manage them. However, little is discussed about the use of extra-narrow implants, specifically. At the patient level, it was reported that systemic diseases, such as diabetes and osteoporosis, are associated with an increased risk of implant failure.[18] However, it was not observed in this study, as no correlation was found between medical conditions and extra-narrow implant loss. On the other hand, smoking habits increased by

Table 4- Relative frequency of implant-related variables and their association with prosthesis loss

Prosthesis loss?		Yes		No		Total		p-value
		N	%	N	%	N	%	
Implant length	10 mm	0	0.0%	11	100.0%	11	100.0%	0.383
	12 mm	1	5.9%	16	94.1%	17	100.0%	
	14 mm	0	0.0%	21	100.0%	21	100.0%	
	15 mm	0	0.0%	0	0.0%	0	0.0%	
Region of implant placement	Lower canines	0	0.0%	1	100.0%	1	100.0%	0.972
	Lower central incisors	1	4.5%	21	95.5%	22	100.0%	
	Lower molars	0	0.0%	2	100.0%	2	100.0%	
	Lower premolars	0	0.0%	3	100.0%	3	100.0%	
	Upper canines	0	0.0%	0	0.0%	0	0.0%	
	Upper lateral incisors	0	0.0%	9	100.0%	9	100.0%	
	Upper premolars	0	0.0%	4	100.0%	4	100.0%	
	Others	0	0.0%	9	100.0%	9	100.0%	
Insertion torque (N.cm)	10–35	0	0.0%	15	100.0%	15	100.0%	0.605
	36–60	1	4.3%	22	95.7%	23	100.0%	
Healing	Yes	0	0.0%	24	100.0%	24	100.0%	0.520
	No	1	3.8%	25	96.2%	26	100.0%	
Prosthesis type	Multi-unit fixed prosthesis	0	0.0%	22	100.0%	22	100.0%	0.338
	Overdenture	0	0.0%	12	100.0%	12	100.0%	
	Single-unit prosthesis	1	6.2%	15	93.8%	16	100.0%	
Time between implant and prosthesis placement	Immediate loading	1	3.0%	32	97.0%	33	100.0%	0.893
	1–4 months	0	0.0%	14	100.0%	14	100.0%	
	5–6 months	0	0.0%	3	100.0%	3	100.0%	
Final prosthesis retention	Cemented	1	6.7%	14	93.3%	15	100.0%	0.348
	Overdenture	0	0.0%	12	100.0%	12	100.0%	
	Screwed	0	0.0%	19	100.0%	19	100.0%	
Any prosthesis repair?	Yes	1	50.0%	1	50.0%	2	100.0%	0.040*
	No	0	0.0%	48	100.0%	48	100.0%	
Peri-implant bone loss?	Yes, more than 1.5 mm	0	0.0%	2	100.0%	2	100.0%	
	No	0	0.0%	43	100.0%	43	100.0%	

*Statistically significant at $p<0.05$.

eight times the chances of extra-narrow implant loss. The tobacco use by patients with dental implants is extensively discussed and, although a study reported that smoking alone could not be considered a risk factor,[19] other authors showed higher risks of implant failure in smokers.[20,21,22]

Regarding implant-related factors, no correlation for implant loss was found. Other authors also observed no differences in narrow implant survival rates among different types of restoration and implant placement,[7] showing that narrow implants are a reliable treatment option, even for challenging maxillary or mandibular rehabilitation. In this study, most implants were inserted in the central and lateral incisors, which are reported to reduce the risk of implant loss, due to the absence of increased occlusal forces.[4]

However, when prosthesis loss was evaluated, a significant association was found with previous need of prosthesis repair. Although similar results were found in a study showing that all lost prostheses had previously underwent laboratory repair,[23] there was only one prosthesis lost in this study, which is not statistically representative.

No correlation was observed between adverse events and implant loss in this study, even though implant failure was associated with the occurrence of local infections by other authors.[7] Since no association was found between implant failure and patient characteristics or adverse events, all implant losses were results of lack of osseointegration, probably related to factors inherent to surgery and individual

Table 5- Relative frequency of patient-related variables and their association with adverse events

Any adverse event occurred after surgery?		Yes		No		Total		OR (CI 95%)	p-value
		N	%	N	%	N	%		
Sex	Woman	1	1.6%	60	98.4%	61	100.0%	0.1 (0.0–1.2)	0.072
	Man	3	12.0%	22	88.0%	25	100.0%	(ref.)	
Presence of thyroid dysfunction?	Yes	0	0.0%	4	100.0%	4	100.0%	ł	0.824
	No	4	4.9%	78	95.1%	82	100.0%	(ref.)	
Presence of coagulation disorders?	Yes	0	0.0%	3	100.0%	3	100.0%	ł	0.861
	No	4	5.0%	76	95.0%	80	100.0%	(ref.)	
Presence of poor healing capacity?	Yes	0	0.0%	1	100.0%	1	100.0%	ł	0.952
	No	4	4.9%	78	95.1%	82	100.0%	(ref.)	
Presence of incomplete jawbone growth?	Yes	0	0.0%	5	100.0%	5	100.0%	ł	0.783
	No	4	4.9%	77	95.1%	81	100.0%	(ref.)	
Regular steroid use?	Yes	0	0.0%	1	100.0%	1	100.0%	ł	0.953
	No	4	4.8%	80	95.2%	84	100.0%	(ref.)	
Previous radiotherapy in the head/neck?	Yes	0	0.0%	1	100.0%	1	100.0%	ł	0.953
	No	4	4.8%	80	95.2%	84	100.0%	(ref.)	
Bisphosphonate therapy?	Yes	0	0.0%	3	100.0%	3	100.0%	ł	0.864
	No	4	4.9%	78	95.1%	2	100.0%	(ref.)	
Psychological limitations?	Yes	0	0.0%	17	100.0%	17	100.0%	ł	0.402
	No	4	5.9%	64	94.1%	68	100.0%	(ref.)	
Presence of bone metabolism disorders?	Yes	0	0.0%	4	100.0%	4	100.0%	ł	0.822
	No	4	4.9%	77	95.1%	81	100.0%	(ref.)	
Smoking?	Yes	0	0.0%	11	100.0%	11	100.0%	ł	0.568
	No	4	5.4%	70	94.6%	74	100.0%	(ref.)	

ł No sufficient sample size to calculate.

healing process.[24]

The mean implant survival time for narrow implants in this study, according to the Kaplan-Meier survival analysis, was slightly greater than seven years, whereas another study reported approximately 4.5 years of survival.[25] However, since this study included only patients treated with overdentures supported by narrow implants, differences in the distribution of occlusal forces must be considered and these results must be analyzed carefully.[26] When implants placed only in smoking patients were evaluated, their mean survival time was cut in half, showing the great effect of tobacco use on dental implant treatment, as observed by other authors.[27] Regarding prosthesis survival, since only one failed, the mean survival time was almost the same as the mean follow-up period, as observed before.[28]

Since retrospective observational studies use data that were originally collected for other purposes, not all relevant information might have been available for analysis, and this is a limitation of this study. There could be missing data due to poor registration quality or variables that were not considered to be registered in advance. In both cases, the origin of missing information can lead to information bias. Moreover, due to this study design, it may be difficult to assess the temporal relationship between data found, leading to a potential confounding bias. Information related to date of implant and prosthesis placement were collected, as well as concerning risk factors. This information was important to analyze some temporal correlations, such as time to implant or prothesis loss. Analyses of the correlation between patient characteristics and parameters of interest may also minimize confounding bias.

Conclusion

High implant and prosthesis survival rates were found in the long term for treatment with extra-narrow implants, showing that they are a reliable option to rehabilitate regions with limited space. Moreover, a significant correlation was observed between smoking

Table 6- Relative frequency of implant-related variables and their association with adverse events

Any adverse event occurred after surgery?		Yes		No		Total		OR (95% CI)	p-value
		N	%	N	%	N	%		
Implant length	10 mm	0	0.0%	17	100.0%	17	100.0%	ł	
	12 mm	2	5.1%	37	94.9%	39	100.0%	0.7 (0.1–5.3)	0.733
	14 mm	2	7.1%	26	92.9%	28	100.0%	(ref.)	
Region of implant placement	Lower canines	0	0.0%	4	100.0%	4	100.0%	ł	
	Lower central incisors	3	8.6%	32	91.4%	35	100.0%	1.7 (0.2–17.4)	0.660
	Lower molars	0	0.0%	3	100.0%	3	100.0%	ł	
	Lower premolars	0	0.0%	7	100.0%	7	100.0%	ł	
	Upper canines	0	0.0%	1	100.0%	1	100.0%	ł	
	Upper lateral incisors	1	5.3%	18	94.7%	19	100.0%	(ref.)	
	Upper premolars	0	0.0%	7	100.0%	7	100.0%	ł	
	Others	0	0.0%	10	100.0%	10	100.0%	ł	
Insertion torque (N.cm)	10–35	0	0.0%	22	100.0%	22	100.0%	ł	0.158
	36–60	4	10.3%	35	89.7%	39	100.0%	(ref.)	
Healing	Yes	3	7.0%	40	93.0%	43	100.0%	3.1 (0.3–30.8)	0.317
	No	1	2.4%	41	97.6%	42	100.0%	(ref.)	
Prosthesis type	Multi-unit fixed prosthesis	2	4.8%	40	95.2%	42	100.0%	0.6 (0.1–4.4)	0.591
	Overdenture	0	0.0%	13	100.0%	13	100.0%	ł	
	Single-unit prosthesis	2	8.0%	23	92.0%	25	100.0%	(ref.)	
Final prosthesis retention	Cemented	1	6.7%	14	93.3%	15	100.0%	(ref.)	0.348
	Overdenture	0	0.0%	12	100.0%	12	100.0%	ł	
	Screwed	0	0.0%	19	100.0%	19	100.0%	ł	
Any prosthesis repair was reported?	Yes	1	50.0%	1	50.0%	2	100.0%	(ref.)	0.055
	No	0	0.0%	48	100.0%	48	100.0%	ł	
Periimplant bone loss?	Yes, more than 1.5 mm	1	16.7%	5	83.3%	6	100.0%	(ref.)	
	No	0	0.0%	56	100.0%	56	100.0%	ł	

ł No sufficient sample size to calculate.

Table 7- Mean, standard deviation, and 95% confidence interval of implant and prosthesis survival, based on Kaplan-Meier survival curves

	Mean survival rate (years)	Standard deviation	95% inferior confidence interval	95% superior confidence interval	p-valor between factors
All implants	7.098	0.197	6.713	7.484	-
All prostheses	6.282	0.125	6.037	6.527	-
Implants in smokers	3.765	0.394	2.99	4.537	0.002*
Implants in non-smokers	7.255	0.17	6.92	7.588	-

*Statistically significant at $p<0.05$.

and implant loss. Since the retrospective design of this study presented some limitations, further prospective studies must be conducted to confirm its results.

Conflict of interest

The authors Elcio Marcantonio Junior and Ivete Sartori are consultants for Neodent. The authors Camila Vianna, Roberta Rocha, Waleska Caldas and Larissa Trojan work for Neodent/Straumann Group.

Authors' contributions

Marcantonio Junior, Elcio: Investigation (Equal); Supervision (Lead); Writing – review & editing (Equal). **Sartori, Ivete Aparecida de Mattias:** Investigation (Equal); Supervision (Equal); Writing – review & editing (Equal). **Vianna, Camila Pareira:** Data curation (Equal); Investigation (Lead); Writing – original draft (Equal). **Rocha, Roberta Schroder:** Writing – original draft (Equal). **Caldas,**

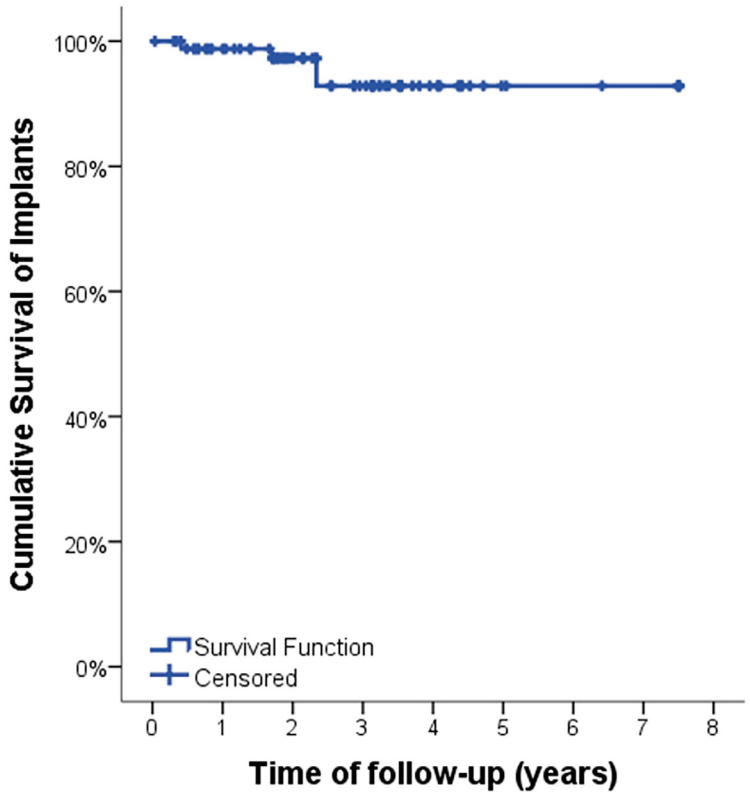

Figure 1- Kaplan-Meier implant survival curve

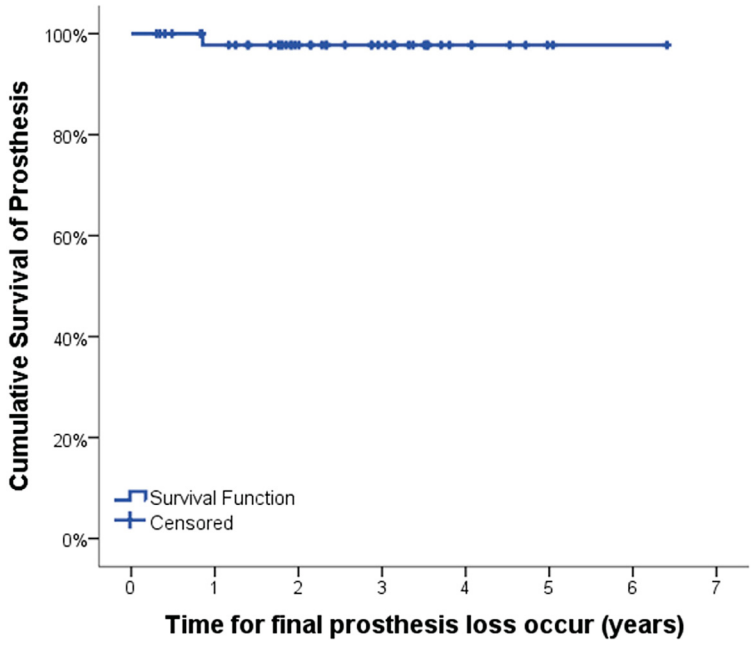

Figure 2- Kaplan-Meier prosthesis survival curve

Waleska: Formal analysis (Lead); Writing – review & editing (Equal). **Trojan, Larissa Carvalho:** Conceptualization (Equal); Project administration (Equal).

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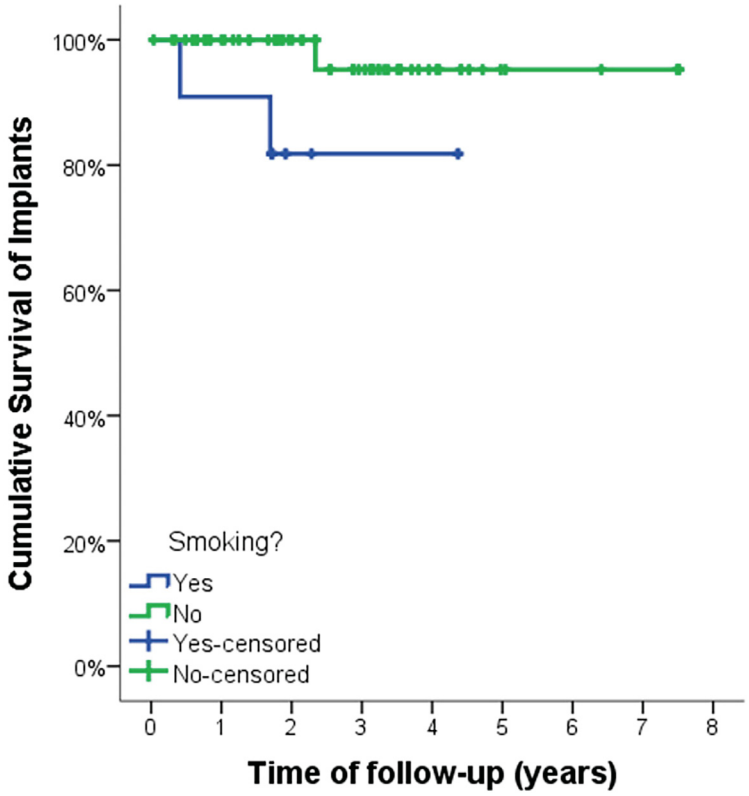

Figure 3- Kaplan-Meier implant survival curve according to smoking habits

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