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

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Aim: This study aimed to analyze if polymorphisms of metalloproteinases can influence endosseous implants' osseointegration failure. **Methods:** This meta-analysis was registered in PROSPERO (CRD42020172108). The literature search was performed on Pubmed/MEDLINE, EMBASE, Scielo, BVS (LILACS and BVS Odontology), and Cochrane Controlled Trials databases. The gray literature and a manual search in periodicals of specific relevance to dentistry and the orthopedics field were also performed. Two calibrated reviewers read all titles and abstracts of the articles and selected those related to the theme. Then, the authors reviewed the full selected articles, fulfilling the inclusion and exclusion criteria. The inclusion and exclusion criteria were related to the type of study design, article language, and population characteristics. The quality of individual studies was evaluated using the Newcastle-Ottawa scale. A meta-analysis was performed using the MetaGenyo software to analyze the association between MMP SNPs and the risk of implant osseointegration failure. The Fixed Effects Model (FEM) and Random Effects Model (REM) were used depending on the amount of heterogeneity in the data. **Results:** Three hundred ninety-seven articles were screened, and nine studies were selected for 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 the Caucasian population (OR=6.88, 95% CI=3.48-13.59) while in the 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:** Even considering the limitations, our study suggests that some polymorphisms of metalloproteinases can be involved in the risk of osseointegration failure.

Keywords: Genetic association studies. Matrix metalloproteinases. Polymorphism, genetic. Osseointegration. Dental implantation, endosseous.

Introduction

Osseointegrated implants have been considered the most functional alternative to dentistry and orthopedic therapies, as they can provide predictable, reproducible, and durable results. Despite the long-term success shown by longitudinal multicenter studies, failure is inevitable, with aseptic loosening being one of the main failures

Dental and orthopedic 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 occur 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 pattern of bone loss is similar since in dental and orthopedic implants the process begins in the proximal area of the implant and progresses 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 essential 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 proteins related to 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), contribute to biological variation and affect how each individual responds to processes and diseases. Some SNPs may influence osteogenesis and inflammatory responses, explaining some of the interindividual risk factors in osseointegration.

Since the sample size in the studies that evaluated the influence of MMP SNPs in osseointegration failure is limited and different SNPs can be involved in osseointegration failure, this systematic review is important to give an overview of published studies. Additionally, the meta-analysis is necessary to perform the statistical combination of the results of these multiple studies to provide more confidence in the association of MMP SNPs and osseointegration failure. Thus, this systematic review and meta-analysis to identify MMP SNPs' contribution to the risk of osseointegration failure, including dental and orthopedic 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 PECO question that guided this study was (1) population: patients with implant placed; (2) exposition: patients with the specific alleles of MMP SNPs (risk allele or without protective allele); (3) comparison: patients without specific alleles of MMP SNPs (with protective allele or without risk allele); (4) outcome: risk of osseointegration failure. In this way, 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 May 15th, 2024 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 journals of specific relevance to the area of dentistry and orthopedics were also performed. The journals searched were The International Journal of Oral & Maxillofacial Implants, Journal of Oral and Maxillofacial Surgery, Brazilian Journal of Oral Sciences, Implant Dentistry, Clinical Implant Dentistry and Related Research, Journal of Orthopaedic Research, Journal of Orthopaedic Surgery and Research, Journal of Orthopaedics and Traumatology and Journal of Orthopaedics. For the search terms, the Boolean operators 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) read all the articles' titles and abstracts and selected those related to the theme. This step was blinded, and in case of any discrepancies, both authors discussed them andreached a consensus. Rayyan QCRI software was used to help in the screening step.

The authors then reviewed the fully selected articles, fulfilling the inclusion and exclusion criteria independently and blindly. In case of any discrepancies, the third reviewer (MCLGS) 's opinion resolved them.

Eligibility criteria

The following inclusion criteria were applied:

(1) Study in humans;

(2) Patients who received dental and/or orthopedic 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 in languages other than English, Portuguese, and Spanish.

The eligibility criteria were selected based on the PECO question. The population was patients who had sufficient age and health conditions to have dental and orthopedic implants placed. We considered the PCR-RFLP, PCR, or PCR + fluorescence emission methods valid methods to analyze the presence or absence of specific alleles of MMP SNPs (risk allele or protective allele).

The failure criteria for dental implants were presenting mobility and pain. The failure criteria for total arthroplasty were clinical, radiological, laboratory, and intrasurgical diagnosis of aseptic loosening in the first 5 years after surgery.

We decided to include only case-control study designs. This is the appropriate design to evaluate risk factors, as it compares a group of participants possessing a condition of interest to a similar group lacking that condition. Most studies that evaluated polymorphism as a risk factor are case-control. The risk of osseointegration should be presented in a contingency table reporting the existence or absence of the specific alleles of MMP SNPs in the test group (patients with implant failure) and control group (patients with implant success).

Data extraction

Data extracted from each study were analyzed and sorted by two independent authors (RSR and AHPG), in case of any discrepancies, both authors discussed and reached a consensus. The kappa index was 1.0. 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. If needed, the authors were contacted by email to provide more information.

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 authors (RSR and AHPG) independently assessed the risk of bias in the included studies. In case of any discrepancies, the opinion of the third reviewer author (AGS) resolved them.

Statistics

The MetaGenyo software was used to evaluate the association between MMPs SNPs and the risk of implant osseointegration failure[19]. To guarantee the results, the meta-analysis was also performed in R software with the metafor package. Since there was no difference between the results, only MetaGenyo results are shown in this article.

The P-value for Hardy Weinberg Equilibrium (HWE) was calculated in controls. As the analysis comprises several studies, the P-values were adjusted by the Benjamini and Hochberg false discovery rate (FDR) method of the χ^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 have already been described in MMP genes. In this study, we evaluated five SNPs in MMPs, which 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 I^2. I^2 values above 50% indicated significant heterogeneity, indicating using 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 the major allele and B represented the 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 the 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 397 articles were rescued from the databases, with no additional articles found on the other sources. After duplicate removal, title and abstract screening, thirteen studies were fully analyzed against the inclusion and exclusion criteria. Nine studies were included in the systematic review to fill all the requirements, resulting in nine polymorphic sites.

The other four studies were excluded due to be related to other outcome than implant failure[20-22] and do not evaluate MMP SNPs[23]. In meta-analysis four polymorphic sites were excluded because the data were from a single article.

Table 1 shows an overview of the articles included in the meta-analysis. Regarding the evaluated SNPs, three different MMPs were considered, including two collagenases (MMP-1, MMP-8) and one stromelysin (MMP-3). Also, three other SNPs related to the MMP-1 were evaluated. 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 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, and only in two studies from peripheral blood. Regarding the genotyping method, a Polymerase Chain Reaction was used, followed by restriction endonuclease digestion and dual-labeled probes in real-time PCR or fluorescence emission.

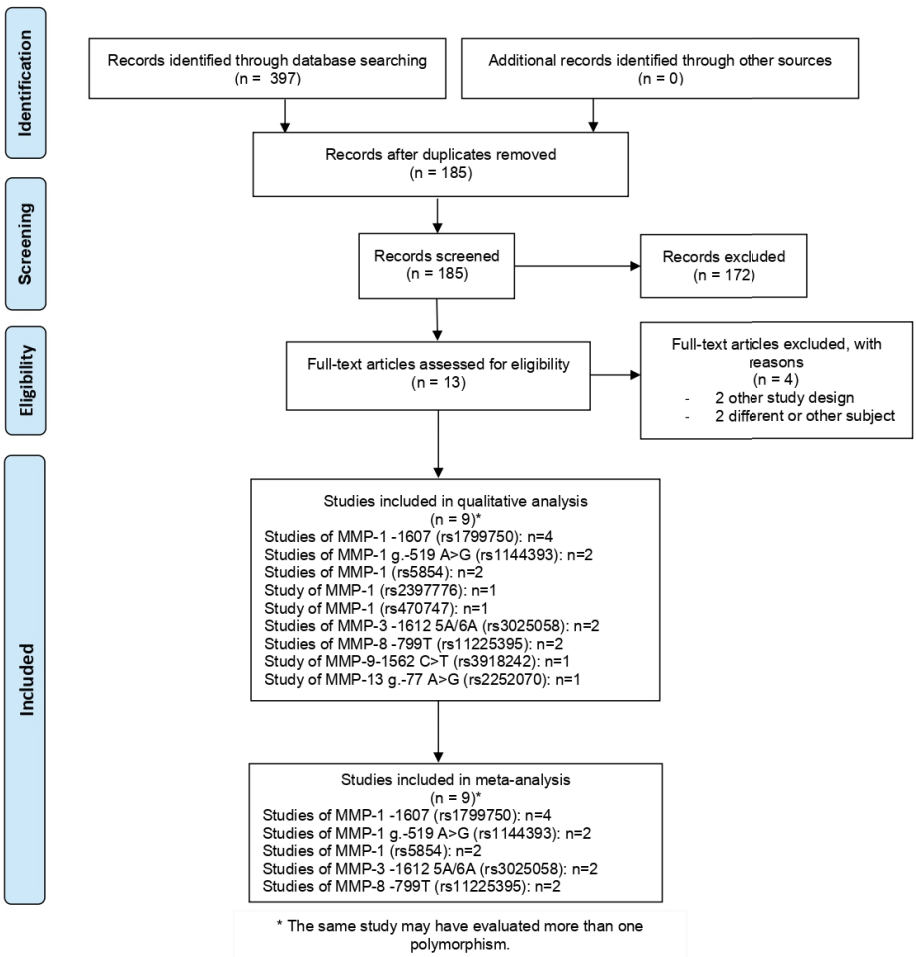

Figure 1. PRISMA flow diagram

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 et al.[24]	2018	Latin American	Brazil	Dental Implant	200	46	39	15	32	55	13	0.158	0.316
	Leite et al.[25]	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 et al.[24]	2018	Latin American	Brazil	Dental Implant	200	33	58	9	63	31	6	0.4144	0.4144
	Godoy-Santos et al.[26]	2009	Latin American	Brazil	Total Hip Implant	58	0	9	18	21	7	3	0.076	0.1013
	Leite et al.[25]	2008	Latin American	Brazil	Dental Implant	104	15	24	5	37	16	7	0.0252*	0.0504
	Santos et al.[27]	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 et al.[28]	2014	Asian	China	Total Hip Implant	144	36	18	9	64	14	3	0.0699	0.1398
	Malik et al.[29]	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 et al.[30]	2016	Latin American	Brazil	Dental Implant	240	29	67	24	40	58	22	0.9034	0.9034
	Munhoz et al.[24]	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 et al.[24]	2018	Latin American	Brazil	Dental Implant	200	63	25	12	36	48	16	1	1
	Costa-Junior et al.[31]	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 Collagenase-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 glands, macrophages, neutrophils, and keratinocytes.	cathepsin G, elastase, kallikrein, kinase, plasmin, tryptase.	MMP-1, MMP-8, MMP-9, MMP-13
MMP-8 Collagenase-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.[32], 2016.

Table 3 shows the quality assessment of case-control studies included in this systematic review and meta-analysis. Most of the studies had a low risk of bias.

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.[33]	2019	★★	★★	★★★	7
Munhoz et al.[24]	2018	★★	★★	★★★	7
Munhoz et al.[30]	2016	★★	★★	★★★	7
Yan et al.[28]	2014	★★	★★	★★★	7
Costa-Junior et al.[31]	2013	★★	★	★★★	6
Godoy-Santos et al.[26]	2009	★★	★	★★★	6
Leite et al.[25]	2008	★★	★	★★★	6
Malik et al.[29]	2007	★★	★★	★★★	7
Santos et al.[27]	2004	★★	★	★★★	6

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 assessed 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. Orthopedic implants included total hip arthroplasty, with at least 183 failure implants.

Dental implant success was considered evaluating implant immobility, the health of peri-implant tissues, function, and patient comfort. The diagnostic criteria used to assess dental implant failures were presenting mobility and/or pain.

The total hip arthroplasty was considered successful when the implant remained clinically asymptomatic for more than five years and showed no radiographic features of aseptic loosening. Early failure was a clinical, radiological, laboratory, and intrasurgical diagnosis of aseptic loosening in the first five 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. They did not have any of the following exclusion criteria: smokers, a history of diabetes or osteoporosis, hepatitis or HIV infection, immunosuppressive chemotherapy, or a history of any disease known to compromise immune function severely. Patients who were submitted to a precocious prosthesis load or regenerative surgery, such as bone grafting, and have had postsurgical complications, such as infection were also excluded. 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 of age- and gender-matched patients. Dental implant patients showed an average age of 49 years ± 10 (18–80), a prevalence of females (65%), and a prevalence of maxillary implant (61% and mean of 4.6 implants by patients). The mean follow-up time was seven years (minimum one year and maximum 18 years). Total hip arthroplasty patients showed an average age between 57 and 72 years and proved therapeutically successful over long-term follow-up (at least ten years).

Meta-analysis results

Five SNPs were included in the meta-analysis. They were previously identified and included in the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/SNP/) database with minor allele frequencies greater than 0.15. The genotype distributions of all the included studies were in accordance with HWE, except for Leite et al.[25], 2008 and Santos et al.[27], 2004 (Table 1).

Table 4 shows the main results of the meta-analysis. The association between five MMPs and osseointegration failure was evaluated in two comparison models: a recessive model and an allele contrast. Subgroup analysis was performed according to 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 sub-

group analysis was performed because 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: I^2=67%, *p*=0.03; 1G vs 2G: I^2=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 was performed due to the high heterogeneity in the overall (CC vs. CT + TT: I2=97%, p=0; C vs. T: I^2=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.

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*

Continue

Continuation

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.

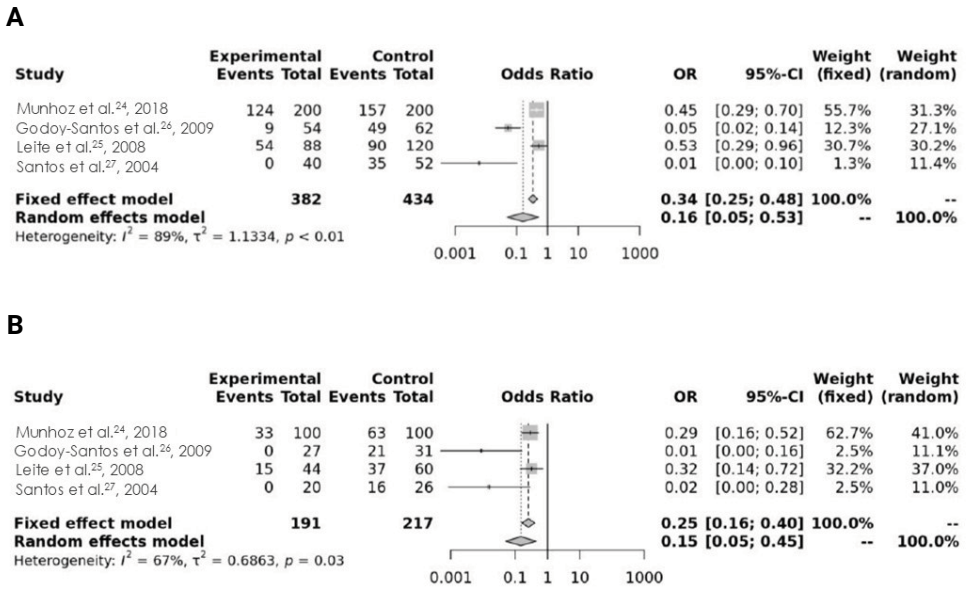

Figure 2. a) Forest plot for the association between osseointegration failure and MMP-1 g.-1607 G>GG (rs1799750) polymorphism in allele contrast comparison. b) Forest plot for the association between osseointegration failure and MMP-1 g.-1607 G>GG (rs1799750) polymorphism in the recessive model. The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

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 comparisons also do not show an association.

Both models, recessive and allele contrast, in the MMP-8 g.-799 C>T (rs11225395) SNP were statistically associated with osseointegration 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).

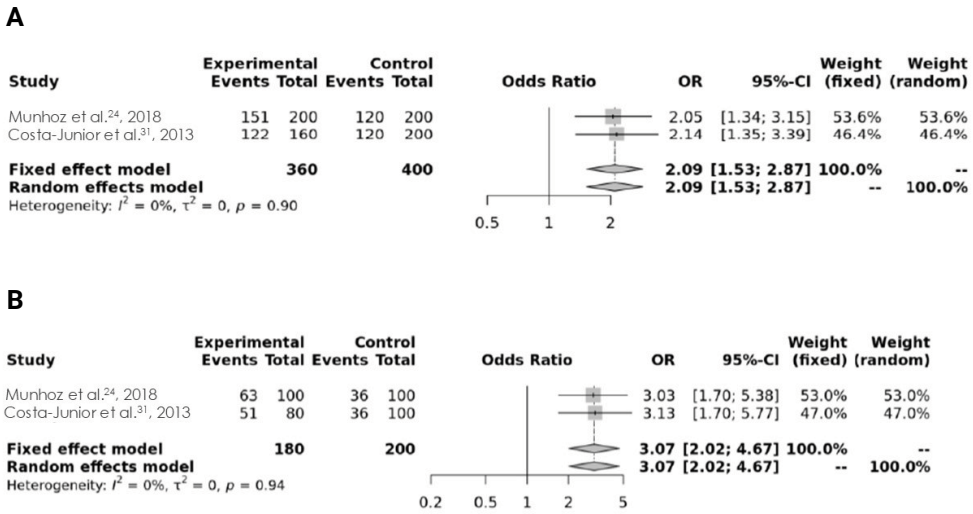

Figure 3. a) Forest plot for the association between osseointegration failure and MMP-8 g.-799 C>T (rs11225395) polymorphism in allele contrast comparison. b) Forest plot for the recessive model's association between osseointegration failure and MMP-8 g.-799 C>T (rs11225395) polymorphism. The analyses were based on the number of patients with implant failure.

Sensitivity analysis

A sensitive analysis was performed to visualize if any study contributed significantly more 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 to 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.[24] and Santos et al.[27] were omitted in both genetic models in the overall comparison.

Discussion

Some studies revealed the existence of clustering of implant failure[34-36], with multiple implant failures 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 in a higher chance of osseointegration problems.

For example, smoking can impair bone and wound healing[37], 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[37]. 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[38,39]. The younger age and avascular necrosis are risk factors that could increase the occurrence of aseptic loosening of the total hip implant[40]. The higher incidence of aseptic loosening in young patients is probably due to the more significant 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[41]. Thus, all studies evaluated in this meta-analysis presented strict sample selection criteria, reducing the interference of risk factors that could mask or increase the real role of SNPs.

Another important point is the need to treat implant failure types 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. Besides, aseptic failure presents particular characteristics, being aseptic loosening that arises from aseptic inflammatory reactions to the prosthetic implants major cause of all total hip arthroplasty failure. 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[42,43].

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) overall analysis showed an 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 dental and total hip implant failure. This SNP is located in the promotor region of the MMP gene and is related to the expression and activity of the MMP-1 enzyme[44], 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 MMP-1 expression or activity due to the presence of a specific allele in this SNP could explain a more intense degradation of collagen that interferes significantly with 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[45] and the development of temporomandibular joint osteoarthritis and osteoarthritis in people aged less than 60 years[46]. Baroneza et al.[47] (2014) 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 of having a rotator cuff tear injury[44], knee osteoarthritis[48-50] and osteomyelitis[51]. In addition, oral and oropharyngeal squamous cell carcinoma, when associated with tobacco and alcohol, also had a relationship with this SNP[52].

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[53-55]. However, this SNP was associated with the risk of development of osteomyelitis[51] and tendinopathy[47,56].

Finally, in the overall analysis, the MMP-1 g. 3' UTR C>T (rs5854) also showed no 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. Studies with this SNP are rare in the literature, but one study showed that a person with this SNP has a higher chance of developing oral squamous cell carcinoma[57].

The studies that analyzed the SNP MMP-3 g.-1612 5A>6A (rs3025058) showed that this SNP is not related to osseointegration failure, which is corroborated by the results of this meta-analysis, which 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[58]. This SNP was associated with a decreased susceptibility to chronic periodontitis, especially in Asian populations, and a decrease in the risk of aggressive periodontitis in Asians[59]. 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[60] and increased susceptibility to developing oral submucous fibrosis and head and neck squamous cell carcinoma[61].

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 on this SNP, and two of them showed an association with posterior tibial tendon insufficiency and pathogenesis of atherosclerosis[56,62]. Moreover, Weng et al.[63] (2016) performed a meta-analysis and found a higher risk of developing periodontitis when an MMP-8 g.-799 C>T (rs11225395) SNP is present, and it is known that non-treated periodontitis can culminate in a dental implant loss.

Accordingly, the MMP-8 is involved in periodontal destruction because of its collagenase activity. This relationship can explain why patients with an SNP in MMP-8 have more risk of developing implant failure[6,64,65].

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 significant heterogeneity was evident in this meta-analysis. Nevertheless, stratified analysis by ethnicity and type reduced heterogeneity significantly. The genotype distributions of SNPs vary in different ethnicities and must be evaluated carefully. Besides, 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 essential to include more studies in different populations to understand the real role of the MMP SNP in implant failure. Additionally, the studies have a low risk of bias as analyzed using the Newcastle-Ottawa tool, reinforcing the quality of data included in this meta-analysis. Even considering these limitations, the data of this meta-analysis can be used as a guide for genetic identification of individuals at higher risk of loss implant can contribute to strategies of modulation of the genetic markers and ensure personalized therapy.

In conclusion, besides its limitation regarding a low number of studies and patients, this meta-analysis showed higher risks of osseointegration failure when the MMP-8 g.-799 C>T (rs11225395) SNP is present. Regarding the MMP-1 g. 3' UTR C>T (rs5854) SNP, the Caucasian population with this SNP has a higher chance of osseointegration failure, and the Asian population is protected from osseointegration failure. The MMP-1 g.-1607 G>GG (rs1799750) is an SNP that protects the person from osseointegration failure. Ultimately, the MMP-1 g.-519 A>G (rs1144393) and MMP-3 g.-1612 5A>6A (rs3025058) showed no association with osseointegration failure.

Data Availability

Datasets related to this article will be available upon request to the corresponding author.

Conflicts of interest

The authors declare there are no conflicts of interest.

Author Contribution

Roberta Schroder Rocha: Conceptualization, Methodology, Formal Analysis and Writing – Original Draft Preparation. **Ana Helena Pereira Gracher:** Formal Analysis and Writing – Review & Editing. **Alexandre Godoy-Santos:** Formal Analysis and Writing – Review & Editing. **Walter Ricioli Junior:** Writing – Review & Editing. **Maria Cristina**

Leme Godoy dos Santos: Conceptualization, Formal Analysis, Writing – Review & Editing and Supervision. All authors actively revised and approved the final version of the manuscript.

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