Clin Oral Invest (2013) 17:311–316
DOI 10.1007/s00784-012-0699-z

ORIGINAL ARTICLE

Influence of MMP-8 promoter polymorphism in early osseointegrated implant failure

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Received: 6 October 2011 / Accepted: 17 February 2012 / Published online: 2 March 2012

Abstract
Objective Dental implants consist in the treatment of choice to replace tooth loss. The knowledge that implant loss tends to cluster in subsets of individuals may indicate that host immuneinflammatory response is influenced by genetic factors. In fact, genetic polymorphisms influence the osseointegration process. The objective of this study was investigate the possible relationship between C-799T polymorphism in matrix metalloproteinase 8 (MMP-8) gene and early implant failure in nonsmoker patients.
Methods and materials Subjects were divided into two groups: control group (100 patients with one or more healthy implants) and test group (80 patients that had suffered one or more early implant failures). Genomic DNA from oral mucosa was amplified by PCR and analyzed by restriction endonucleases. The significance of the differences in observed frequencies of polymorphisms was assessed by Chi-square.
Results Statistical analysis shows that in the MMP-8 gene, the T allele in 76.25% in the test group and the T/T genotype, 63.75% in the same group, may predispose to early loss of implants osseointegrated.
Conclusion These results suggest that polymorphism in the promoter region of MMP-8 gene is associated with early implant failure. This polymorphism can be a genetic marker to risk of implant loss.
Clinical relevance The determination of this genetic pattern in osseointegration would enable the identification of individuals at higher risk to loss implant. Thus, genetic markers will be identified, contributing to an appropriate preoperative selection and preparation of strategies for prevention and therapy individualized to modulate the genetic markers and increase the success rate of treatments.

Keywords MMP-8 · Polymorphism · Implant failure · Osseointegration · T allele · Risk factors

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Introduction

Osseointegrated dental implants have been considered the most esthetic and functional alternative to missing teeth as they can provide predictable, reproducible, and durable results [1, 2]. Despite the long-term success shown by longitudinal multicenter studies [1–3], failure is inevitable. Implant therapy has become a common practice and will probably gain popularity during the next several years; this implies that the frequency of implant failure and related complications tend to increase [4].

Implant losses can arbitrarily be divided into early, when osseointegration fails to occur, and late losses, when the achieved osseointegration is lost after a period of function [5]. The cluster phenomenon, multiple implant failures in the same subject, supports the evidence that individual characteristics play an important role in the early failure process [6]. However, little is known about the influence of genetic susceptibility on osseointegration.

Gene polymorphisms are a mechanism by which individuals may exhibit variations within the range of what is considered biologically normal [7]. Polymorphisms in metalloprotease genes have been associated with several pathologies [8–14].

Matrix metalloproteinases (MMPs) represent the major class of enzymes responsible for extracellular matrix metabolism [15]. MMPs are zinc-dependent metallopeptidases belonging to the subfamily M10A which are collectively capable of cleaving virtually all extracellular matrix substrates, including collagens, laminin, fibronectin, vitronectin, and proteoglycans [16]. Like other peptidases in subclan MA(M), the peptidases of family M10 are synthesized as inactive precursors (zymogens), and their activation occurs in the tissue by cleavage of the N-terminal pro-peptide domain by other proteinases [17].

MMPs have important roles in diverse physiological and pathological processes as they regulate various cell behaviors such as angiogenesis, cell proliferation, apoptosis, alteration of cell motility, effects on the immune system and host defense, and modulation of the bioactivity of chemokines [18]. In fact, MMPs are expressed in response to specific stimuli by resident connective tissue cells as well as the major inflammatory cell types that invade the tissue during remodeling events [15], inclusive in implant osseointegration.

Previous studies have also shown that MMPs are present in peri-implant sulcular fluid [19–25] and can play a pathologic role in peri-implant bone loss [21, 26, 27].

The finding of genetic markers related with early implant failure could allow the identification of susceptible individuals to implant loss. The purpose of this study was to investigate the frequencies of the polymorphism in the promoter of MMP-8 gene in individuals with failure of implant so as to verify a possible relationship between this polymorphism and early failure of osseointegrated oral implants.

Material and methods

Subject selection

A sample of 180 non-smoking subjects, >18 years of age, was recruited for study from the patient pool at the Dental Clinics of the Faculty of Dentistry of Piracicaba, University of Campinas, Piracicaba, São Paulo, Brazil; Latin American Institute for Dental Research, Curitiba, Paraná, Brazil; and private implantology clinic in Sao Paulo, Bahia, Paraná, Brazil. The rate of implant loss of these centers was less than 5%. All patients were advised previously about the nature of the study and signed a consent form within a protocol approved by an Institutional Review Board (Ethical Committee in Research at FOP-UNICAMP, protocol 006/2002).

All subjects were in good general and oral health and did not have any of the following exclusion criteria: a history of diabetes or osteoporosis, hepatitis or HIV infection, immunosuppressive chemotherapy, and 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. These strict criteria in obtaining the samples aim to reduce the influence of systemic factors in the loss of the implant to analyze the influence of the polymorphism alone.

The groups were matched by gender and age, with 66% female and mean age of 51(range, 18–80). Subjects were divided into two groups:

1. Control group: 100 patients with one or more healthy implants. These patients had at least one implant that had been implanted for a minimal period of 9 months.
2. Test group: 80 patients that had suffered one or more early implant failures. The implants were considered early lost when presented mobility and/or pain before or during the abutment connection and needed to be removed.

Sampling and DNA extraction

The sampling of epithelial buccal cells was performed as described by Trevilatto and Line [28] and DNA extraction by Aidar and Line [29]. DNA was estimated by measurements of OD 260/280.

Polymerase chain reaction and restriction endonuclease digestion

The MMP-8 genotype was determined by the PCR-RFLP assay. The PCR primers used for amplifying the MMP-8 polymorphism were: forward primer 5′-CAGAGACT CAAGTGGGA-3′ and reverse primer 5′-TTTCATTTGTG GAGGGGC-3′. PCR was carried out in a total volume of 10 μl, containing 400 ng genomic DNA, *taq Green* (Amersham Pharmacia Biotech, Uppsala, Sweden), and 200 nmol of each primer. A 6-μl aliquot of PCR products was then digested with 1 unit of *Sfc*I enzyme at 37°C overnight; this enzyme

cleaves the PCR product into two fragments when the polymorphic site contains allele C (but not T).

Gel electrophoresis

The total amount aliquot of the digest was electrophoresed on a 10% vertical non-denaturing polyacrylamide gel at 20 mA. Gel electrophoresis separates DNA fragments from one another according to size. An electric current repels a mixture of the negatively charged DNA fragments through microscopic pores in the gel from the negative to the positive electrode. Upon completion, the separated fragments of DNA were visualized as a ladder of small bands in the gel by staining with ethidium bromide. The C allele was represented by a DNA band of 106 base pairs, the T allele was represented by a DNA band of 74 base pairs, while the heterozygote showed a combination of both alleles (106 and 74 base pairs; Fig. 1).

Statistical analysis

The significance of the differences in observed frequencies of polymorphism in both groups was assessed by the Chi-squared test. $P<0.05$ was considered statistically significant.

Results

The primers used were efficient to amplify the fragment, and the *Sfc*I enzyme digestion cleaves the PCR products in two fragments when the polymorphism site contains allele C (but not T). On electrophoresis, the C alleles were represented by DNA bands of 74 and 32 bp, the T alleles were represented by a DNA band of 106 bp, whereas the heterozygote displayed a combination of both alleles (106, 74, and 32 bp).

There was a significant difference in the presence of the different alleles between the control group and test group for the MMP-8 gene ($p=0.0011$). The genotype C/T was found in 48% of the control group, while in 63.75% of patients of the test group was observed the genotype T/T ($p=0.0009$). The frequencies of different alleles and genotype of the MMP-8 gene are shown in Table 1.

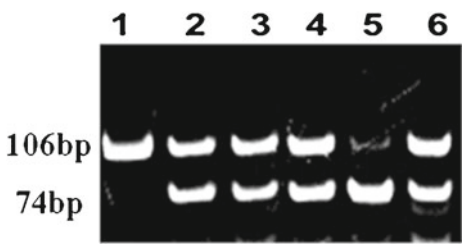

Fig. 1 Gel electrophoresis showing different alleles. *1* genotype T/T, *2*, *3*, *4* genotype C/T, *5* genotype C/C, *bp* fragment size in base pairs

Table 1 Distribution of the MMP-8 allele and genotype in the control and test group

MMP-8 (−799)	Control group, *n* (%)	Test group, *n* (%)	Chi-squared
Allele	*n*=200	*n*=160	
C	80 (40)	38 (23.75)	$p=0.0011$
T	120 (60)	112 (76.25)	
Genotype	*n*=100	*n*=80	
C/C	16 (16)	09 (11.25)	
C/T	48 (48)	20 (25.00)	$p=0.0009$
T/T	36 (36)	51 (63.75)	

Discussion

An abnormal immune response involving different cell types such as macrophages, polymorphonuclear neutrophils, T and B lymphocytes, endothelial cells, fibroblasts, keratinocytes, osteoclasts, and osteoblasts can destroy peri-implant tissues [30–32]. If activated, these cells can synthesize and release cytokines and lipid mediators, which mediate both the inflammatory and the osteolytic processes. Overall, MMPs are likely to cause increased proteolytic tissue destruction in periprosthetic tissue [33]. Since elevated levels of these mediators are present in diseased implant sites, their analysis may provide an effective monitoring of the disease around dental implants.

MMP-8, also known as collagenase-2, was previously discovered, and an exclusive product of neutrophils, but subsequently shown to be expressed by a variety of other cell types such as endothelial cells, smooth muscle cells, macrophages, polymorphonuclear leukocytes, gingival fibroblasts, keratinocytes, chondrocytes, odontoblasts [34–39], and oral cancer cells [4].

Potentially, the MMP-8 degrades type I collagen, contributing to degradation and tissue remodeling [40]. It is an important mediator of destruction in several inflammatory diseases and is related to cardiovascular disease [38], bronchiectasis [41], pulmonary insufficiency [42], periodontitis [43–45], melanomas [46], cancer of the head [47], and healing of diabetics [48]. This MMP is present in peri-implant sulcular fluid [24].

The MMP-8 gene, located on chromosome 11, has functional polymorphisms in the promoter region-799 characterized by a substitution on a cytosine by timina (rs11225395) and has been associated with breast cancer [49]. Since MMP-8 is capable of degrading a large amount of extracellular proteins and influence degradation and remodeling of injured tissues, the study of this gene may be important for a better understanding of the process of osseointegration.

Some studies already show the influence of genetic polymorphisms in implant loss. A polymorphism in the promoter

region of MMP-1 gene is strongly associated with early implant failure in nonsmokers [26]. The same group also suggested that haplotype G-1607GG and A-519G of MMP-1 may be associated with the osseointegration process [27]. The polymorphism G/GG in MMP-1 also was associated with early implant failure of total hip arthroplasty [50]. Montes et al. [51] showed that genotype 2/2 of IL1RN polymorphism was significantly more frequent in patients who presented multiple oral implant losses, which suggests that the clusterization phenomenon has a genetic basis. Dirschnabel et al. [52] investigating the association between IL1B (C-511T) genetic polymorphism and dental implant loss in a Brazilian population and its influence in the clusterization phenomenon suggest no difference between groups with and without implant loss.

In this study, the C-799T polymorphism in the promoter region of MMP-8 gene was associated with early implant failure in nonsmokers. The C/T genotype was observed in most of the control group, while the T/T genotype was more frequent in the test group. Patients bearing this genotype or T allele seem to be more likely to have implant loss. This allele can provide the molecular basis for a more intense degradation of extracellular matrix, which might indicate an increased susceptibility to osseointegration failure. It is important to observe the size of the sample. In fact, early implant failure is not a frequent event, and when smokers are ruled out, the study population is substantially reduced. This is the first study that follows strict exclusion criteria of patients and simultaneously analyzes a large test group; statistical test can show a reliable result.

Genetic polymorphisms probably influence the osseointegration process through the accumulated effect of multiple polymorphisms. To understand the importance of polymorphisms of each allele, it is important to analyze the relative contribution of each polymorphism to the disease phenotype.

Thus, as the relative weight given by each polymorphism seems to be small in complex traits, the investigation of functional candidate genes involved in the physiopathogenesis of osseointegration failure may elucidate the genetic component of implant failure [53]. The determination of this genetic pattern in osseointegration would enable the identification of individuals at higher risk to loss implant. Thus, genetic markers will be identified, contributing to an appropriate preoperative selection and preparation of strategies for prevention and therapy individualized to modulate the genetic markers and increase the success rate of treatments.

Conclusion

These results indicate that the polymorphism in the promoter of the MMP-8 gene could be a risk factor for early implant failure. This polymorphism could be used as a genetic marker for unsuccessful implants. Perhaps, the finding of several genetic markers related with early implant failure could be of clinical value for a precise and early identification of individuals at high risk to implant loss. It could lead to a more strict selection of patients, and in the future, individual therapeutics could be developed, thereby increasing the implant success rates.

Acknowledgments The authors wish to thank Dr. Silvio Sanches Veiga for his assistance. This study was supported by the Fundação Araucária–Curitiba, PR–Brazil.

Conflict of interest The authors declare that they have no conflict of interest.

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