

# The Role of MMP-1 Gene in the Osseointegration of Dental Implant

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**Submission date:** 24-May-2023 02:15PM (UTC+0800)

**Submission ID:** 2100640758

**File name:** MJMHS\_Role\_of\_MMP\_1\_jurnal.pdf (143.64K)

**Word count:** 2526

**Character count:** 14433

## REVIEW ARTICLE

# The Role of MMP-1 Gene in the Osseointegration of Dental Implant

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## ABSTRACT

Dental implant is one of the most common standard therapies to substitute the loss of the teeth. In some cases, the implant therapies outcome was not successful, since there are several causes, which can be caused by infection or the disruption in the osseointegration process. This study aims to present an evaluation of literature regarding the rule of MMP-1 Gene in Osseointegration in Dental Implant. DNA polymorphism is related to the enhancement of the MMP-1 levels that occur in the fluid surrounding the implant associated with osseointegration disruption and periodontitis. MMP-1 gene polymorphism can be identified with disruption of osseointegration, in which its presence could predict individuals who are at high risk of early implant failure.

**Keywords:** MMP-1, Osseointegration, Dental Implant

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## INTRODUCTION

Dental implant have become significant helpful choice and are currently the most picked choice for oral recovery in edentulous and incompletely dentate patients due to its high achievement rate (1). Effectiveness of osseointegration has made a revolution in implantology, making implant, a substitute for the missing natural teeth, a fair missing treatment for the edentulous conditions. Dental implant osseointegration is reproducible and has long-lasting impacts. And in some situations failure is also likely. Implant failures can be called early losses if osseointegration is not achieved, and late losses if osseointegration is skipped after a service period (2). Branemark described osseointegration as the near application of new and modified bone in accordance with the fixture where the connective or fibrous tissue is not interposed at a light microscopic level (3). The numerous implant defects in same topic support the claim that personal characteristics play a significant role in detecting failure initiation. Host factors showed by role of specific immune reaction aggravation and

osseo-disintegration due to minority titanium particle different in each individual (1). In addition this, multiple implant failures in the same patient, the cluster phenomenon, indicate that individual's host response also have a significant role in the implant loss (1).

In relation with individual characteristic, gene polymorphism may exhibit a variation which is considered biologically normal. DNA variations can modify gene expression and function which can increase susceptibility for a disease and affect a person's phenotype(4). DNA polymorphism has recently been observed in several MMP's promoter region including MMP-1. MMP-1 is a major protease that degrades type I collagen, and the increased expression has been associated with implant failure. Different single-nucleotide polymorphism (SNPs) can influence the degree of MMP-1 expression in the promoter region (3,5). This study aims to present an evaluation of literature regarding the rule of the MMP-1 gene in osseointegration in dental implants.

## Osseointegration

The mechanism for osseointegration is very close to that of primary bone healing. There is an inflammatory process followed with hematoma after surgery, then regeneration formed, and eventually bone tissue

replaces the wound. When proper regeneration occurs, the metal surface and bone tissue are in direct contact (3). Implant failure can be characterized by an implant-involved connective tissue, this capsule occurs as the repair process takes place in place of regeneration. Cytokines inevitably cause the migration of fibroblasts to the injury site and their consecutive proliferation. Fibroblasts secrete growing amounts of extracellular matrix (ECM) (3).

#### Matrix metalloproteinase (MMP)

Matrix metalloproteinases (MMP) are a class of zinc-dependent proteolytic enzymes that may be involved in the osseointegration process of dental implants, responsible for extracellular matrix metabolism (6). MMPs are divided into five major groups such as collagenase, gelatinase, stromelysin, membrane form and others like matrilysin. Changes in MMP activity were related to a variety of disease including cartilage loss and bone deterioration in rheumatoid arthritis, osteoarthritis, acute myocardial infarction and carcinogenesis (5). MMP is provided by inflammatory cells which are responsible for the ECM metabolism associated with the processing of collagen (7).

#### MMP-1

MMP-1 is a major MMP family proteinase that specifically degrades type I collagen, a main part of the ECM and many other types II, III, V, IX fibrillary collagens. MMP-1 is important for ECM modeling and remanufacturing (2,5,7). MMP-1 expression is usually low, where MMP-1 is over-expressed, there may be certain pathological problems such as colorectal cancer, bladder cancer, oral carcinoma, hip arthroplasty, occlusive peripheral artery disease, coronary artery disease, and implant failure (5,7). A study from Munhoz, recommended that haplotype G-1607GG and A-519G of MMP-1 might be associated with the osseointegration cycle (1).

#### MMP-1-Polymorphism

Polymorphism describes natural variants of the sequence (alleles), which can occur in more than one type. These occur in at least 1 % of the considered natural biologically and population (5,8). Majority of DNA polymorphism is single-nucleotide polymorphism (SNP) due to one base exchange. Per individual carry-on average 3.55–4.6 million single nucleotide polymorphisms (SNPs) which can be identified as a single nucleotide base modification that occurs in at least >0.5% of the human population (4). Single nucleotide polymorphisms (SNPs) are the most well-known type of DNA variety in the human genome, and polymorphic alleles have been related with increased susceptibility to complex human illnesses (9). Although

the majority of DNA polymorphism is likely to be functionally neutral, a portion of DNA polymorphism may exert both unique effects on regulating gene expression or coded protein function underlying human variations in disease susceptibility and various biological traits (5,8). A single nucleotide polymorphism (SNP) of proinflammatory mediator genes may affect their expression levels or amino acid sequence, and, consequently, the host inflammatory responses. Each variance occurs within a population to some significant degree. Within coding and non-coding gene sequences, or in intergenic regions, SNP may occur (6). SNP within a coding sequence may change the amino acid sequence of the coding polypeptide (nonsynonymous SNP), or not affect the protein sequence (synonymous SNP).

#### DISCUSSION

Inflammation surrounding areas of implant placement is a crucial physiopathological process which allows local tissue damage to be removed and a viable tissue to be substituted (regeneration). Increase in this process of inflammation is directly related to the amount of tissue that may have been replaced. To achieve successful osseointegration of the implant, complete stabilization between the implant and the surrounding bone is required (10). The inter-relation between stability and bone-quality also determine the success of dental implant (4).

Implant failure due to osseointegration may occur multifactorial conditions; individual susceptibility or risk factors, potential host immune responses even under proper bone tissue conditions, material quality and surgical technique also count the survival of dental implant (4). Microbiological, biological, or biomechanical factors may be linked to implant loss, but the reasons and processes of early implant failure remain unclear. An inflammatory disease of tissue supporting tooth or implant called peri-implantitis (6). Common causes of early and late implant failure are in Figure 1. Mechanical damage to the implant or biological causes leading to peri-implantitis and lack of support for the surrounding bone can cause late loss osseointegration (6). Genetic polymorphism is likely to affect the mechanism of osseointegration through the cumulative multiple polymorphic effect (2). Genetic polymorphisms are likely to interfere with the osseointegration mechanism by multiple polymorphisms' cumulative effect (4). Gene polymorphisms in an individual may modulate the severity and progression of inflammation by oral cytokine expression and modulation (9). See figure 2.

Causes of early failure	Causes of late failure
Poor bone quality: type 4 bone posterior upper jaws	Excessive loading
Poor bone quantity: severe alveolar bone resorption	Peri-implantitis
Patient medical condition: AIDS, uncontrolled diabetes mellitus, osteoporosis, corticosteroids, bisphosphonates therapy, etc	Inadequate prosthetic construction
Smoking	
Infection	
Post-insertion pain	
Lack of primary stability	
Inadequate surgery and prosthodontics	

Figure 1 : Common causes of early and late implant

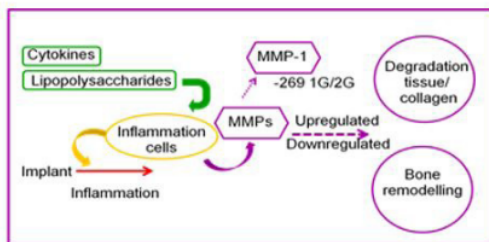


Figure 2 : The mechanism of the possible involvement of polymorphism in MMP-1 related to the degradation of tissue in a dental implant.

In the field of implantology, hereditary polymorphisms in specific cytokines and chemokines have been explored to comprehend why a few individuals show implant flaw regardless of having few risk factors at the time of implant, great bone quality and quantity, no systemic disease or use of drugs, and appropriate also careful surgical-prosthetic planning strategies (9). Implant materials are considered to be inert, and can elevate cytokine levels such as TGF- $\beta$ , IL-1 $\beta$ , and TNF- $\alpha$ . An abnormal immune reaction involving various types of cells, such as T and B lymphocytes, macrophages, polymorphonuclear neutrophils, endothelial cells, keratinocytes, fibroblast, osteoblast, and osteoclast can kill periodontal and peri-implant tissue. When activated, these cells can release cytokines, synthesize and lipid mediators that mediate both osteolytic and inflammatory processes (3).

Implants have also been shown to stimulate the release of pro-inflammatory cytokines by macrophages, such as IL-1 and TNF- $\alpha$ , which mediate the inflammatory and osteolytic process of peri-implantitis and promote the degradation of extracellular matrix components mediated by matrix metalloproteinases(6). Implant material such as titanium, the secretion of TNF- $\alpha$  and IL-1 upon titanium stimulation was significantly higher in patients with implant loss. The data shows that IL-

1/TNF- $\alpha$  in Titanium implant failure is substantially and independently correlated with the release and number of risk genotypes. A genetic risk factor for implant failure may be functional polymorphism in the IL-1 gene. The IL-1 genotype was established in an early study as a clear predictor of vulnerability to serious periodontitis (6).

In addition, inflammatory factors, such as matrix metalloproteinases (MMPs), may influence the balance of other molecules involved in homeostasis of the bone matrix(4). In peri-implant sulcular fluid, matrix metalloproteinases have been identified and play a pathological role in peri-implant bone loss (6). Immunoactivity for MMP-1 was found in the granulation tissue of chronic patients with periodontitis, and the reverse transcriptase-polymerase chain reaction showed that levels of MMP-1 mRNA in inflamed gingival tissue increased significantly; although MMP-8 transcripts also act as neutrophil collagenase only detected at incredibly low levels in diseased gingival tissue. It has been proposed that MMP-1 is likely to become the principal interstitial collagenase in inflamed periodontal tissue (11). Due to its association with increased levels of MMP-1 mRNA in the periapical lesion, the MMP1 - 1607 SNP is known as a risk factor for development of periapical lesions. MMP Polymorphisms genes are extremely related to dental bone pathologies, including bone loss. They also founded in the peri-implant fluid which related to peri-implant diseases (4).

These periapical lesion activity cluster associated cytokines, namely TNF- $\alpha$ , IL-21, IL-17A, and IFN- $\gamma$ , were positively associated with MMP-1 levels (12). Polymorphism -1607 1G/2 G for the MMP-1 gene identified with reduced XmnI and AluI enzymes is a risk factor for the development of chronic periapical lesion; polymorphism can affect the role of MMP-1. MMP-1 plays a crucial role in degrading connective tissue, particularly in the promontory region, in periodontitis (13).

SNPs may have an effect on the level of MMP-1 expressions within the gene promoter. The human gene promoter MMP-1 has found deletion or insertion of guanine at place -269 and produces two separate alleles, one using single guanine and the other two guanines (7). The 2 G allele in MMP-1 polymorphism -269 has potentially increased protein expression levels. This mechanism allows for more severe ECM degradation, which is critical during development and inflammation in tissue remodeling and repair (5,7,8). The 2G and 2G/2G genotypes were substantially more common in patients with severe periodontitis than in the healthy population. The frequency of the G allele and the G/G genotype in the MMP-1-1607 G/G/G were relatively high in patients with one or more early failed implants compared with control group, showing



a relation with early implant failure (6). Leite et al. founded that 28.9 % of patients with earlier implant failure had G / G haplotype (-519)/(-1607) compared to just 12.5 % in the control group and it is stated that G-1607GG polymorphism is strongly associated with early implant failure in non-smokers in the MMP-1 gene. Transcription activity of human MMP-1 showed an increase due to polymorphisms of MMP-1-1607 G/GG (rs1799750) and MMP-1-519 A/G (rs1144393) (6). The findings indicate that the MMP-1 gene may affect the osseointegration process and that patients with higher haplotypes of MMP-1 expression are more likely to experience implant failure due to excessive fibrillary collagen degradation (2).

## CONCLUSION

The injection of guanine at the human MMP-1 gene location -269 produces the 2 G allele which may have been concerned with loss during the osseointegrated dental implant healing process. This polymorphism may be used as a genetic marker to predict or classify individuals at high risk of early implant failure early in life.

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