Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease- A Systematic Review

Burra Anand Deepika1*, Jaiganesh Ramamurthy2
1Postgraduate Student, Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
2Professor and Head, Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical And Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India
*Corresponding author: Burra Anand Deepika, Postgraduate Student, Department of Periodontics, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India, Email: deepikaba93@gmail.com

Submitted: 27 March 2023; Accepted: 16 April 2023; Published: 08 May 2023

ABSTRACT

Background: Periodontal diseases are chronic inflammatory diseases caused by periodontal pathogenic bacteria which is characterised by inflammation and destruction of periodontal tissues. TREM-Triggered Receptor Expressed on Myeloid cells 1(TREM-1) is a cell surface receptors of the immunoglobulin superfamily, involved in the innate inflammatory response to bacterial and fungal infections. TREM-1 activation and expression occur synergistically with TLR as the TREM family contains both inhibitory and activating receptors capable of TLRs moreover , TREM -1 has also been associated with NOD- like receptors (NLR), responsible for sensing microbial danger and amplifying the inflammatory response. On the molecular level, TREM-1 regulates immune cell function, by forming an intracellular complex with signaling adapter DNAX activating protein of 12FDa(DAP12), is involved in immune response to bacterial and fungal infections particularly by amplifying the production of pro- inflammation cytokines by the host.

Aim: The aim of this systematic review is to evaluate the role of Triggered Receptor Expressed in Myeloid Cells 1(TREM -1) in periodontal disease.

Materials And Methods: Source Used And Search Methodology: Electronic databases were done which included studies of the Pubmed, Pubmed central, Medline, Cochrane database of systematic reviews, Mesh, Science direct, Embase databases up till the month of March 2021. The search was performed using key words and terms mentioned in Table. No limits and language restriction were applied during the electronic search to include all the possible clinical trials in the potential relevant article search phase of the systematic review. No time restriction was applied. The search was completed by checking the reference terms and also the key words given in the relevant articles. A manual hand search was also carried out. The articles were screened on the basis of title and abstract. Full text was then downloaded for the relevant articles which fulfilled the inclusion criteria mentioned.

Results: 11 articles were found relevant according to the inclusion criteria .It was found that 11 studies discussed the role of TREM levels in periodontal disease. 5 studies discussed about sTREM-1 levels and IL levels against periodontal pathogens. 1 study showed P1 study showed up Active Matrix
Metalloproteinase (aMMP) Predicts in (TREM -1) In saliva PGLYRP1 AND TREM-1, IL levels in gingival inflammation. 1 study showed TREM-1, mRNA expression in MM6 cells (MONO MAC). 1 study showed TREM -1, TREM-2 in inflamed Human gingiva. 1 study showed TREM -1, PGLYRP 1, MMP 8 in peri implant disease. 1 study showed TREM -1 Response in periodontium in elderly population.

**Conclusion:** The current evidence and results prove that further in the field of TREM could throw a light into the understanding of the inflammatory process of periodontal disease. From the systematic review it is evident that TREM levels are increased in periodontal disease, against periodontal pathogens. Synthetic TREM-1 blockade could mitigate the host inflammatory response and be useful as an adjunct therapy for the treatment of periodontal disease. Further studies are needed to show the specific role of sTERM-1 in inflammatory conditions and diagnostic tests will be available for clinical use in dental practices to assist in patient care. TREM-1 modulation to provide therapeutic effects and arrest the tissue destruction common in periodontitis.

**Keywords:** TREM, TREM -1, Triggering receptor expressed on myeloid cells-1, Periodontitis, Periodontal disease, Levels of TREM

**INTRODUCTION**

Periodontal disease is a multifactorial inflammatory disease resulting from a dysbiotic microbial community of pathobionts and keystroke pathogens which induce the destruction of tissue surrounding the teeth. The primary etiology of this disease remains the imbalance of the oral ecosystem resulting in the predominance of a pathogenic flora belonging to the “red or orange complex” described by socranski. [1] In a mature subgingival biofilm, pathobionts produced an array of virulence factors, antigens or derived products capable of escaping host defense mechanisms and inducing cell and tissue damage through dysregulation of inflammatory response. [2] The regulation of cytokine secretion, in particular IL-1Beta and TNF (Tumour necrosis factor alpha), has been shown to induce periodontal bone destruction through the recruitment and activation of osteoclasts via the increase of RANKL (receptor activator of nuclear factor - kappa B ligand) expression. [3,4] 

Periodontal disease are caused by bacteria commonly arranged in biofilm. In general, the oral cavity can host over 6 billion bacteria from over 700 species (500 of which are able to arrange in biofilms), with up to 200 species present in individual mouth at a given point in time. Oral bacteria are a mix of gram-positive (gm+) and gm- aerobic, anaerobic and facultative anaerobic bacteria; as well as fungi, viruses, mycoplasma and Protozoa.

Dental plaque can be defined as the diverse community of microorganisms found on the tooth surface as a biofilm, embedded in an extracellular matrix of polymers of host and microbial origin. There is a high level of interest in the properties of biofilms and microbial communities across all sectors of industrial, environmental and medical microbiology. [5] Dental plaque accumulates preferentially at stagnant sites that afford protection from the vigorous removal forces that apply in the mouth. Distinct phases of development can be recognized, including:

(a) Adsorption of host and bacterial molecules to the tooth surface
(b) Passive transport of oral bacteria to the tooth surface
(c) Co-adhesion of later colonizers to already attached early colonizers
(d) Multiplication of the attached microorganisms
(e) Active detachment

Oral biofilm in association with anaerobic bacteria is the main etiological factor in periodontal disease. [6] The oral biofilm consists mainly of microbes and host proteins that adhere to teeth within minutes of a dental oral hygiene procedure. The proportions of strict anaerobic, Gram negative and motile organisms increase
Aggregatibacter actinomycetemcomitans A.a., previously Actinobacillus actinomycetemcomitans, is a Gram negative facultative non motile coccoïd bacillus. Its presence in the periodontal pocket is associated with preadolescent, localized juvenile and advanced adult aggressive periodontal disease

Several virulence factors are reported: the leukotoxin is the most important, cytolethal distending toxin, immunosuppression factors, inhibition of PMNS functions etc. Prevotella intermedia, former Bacteroides intermedius, is a black pigmented Gram negative bacterium. This species resists phagocytosis, probably by virtue of its capsule. P.i is an important periodontal pathogen, in association with P.g and A.a Fusobacterium nucleatum-F.n. is an important periodontal pathogen, particularly in the beginning of the rapidly progressive periodontal disease. It creates very strong lipopolysaccharide as well as butyric acid as a metabolic end product.

Bacteroides forsythus - Tannerella forsythensis (T.f) - formerly Bacteroides forsythus - is a non-pigmented saccharolytic anaerobic gram-negative rod. T. f possesses several virulence factors including the production of a trypsin-like protease and lipopolysaccharide.

Capnocytophaga species- Capnocytophaga are microaerophilic Gram negative rods. In host defense mechanism Cells of the immune system and their interactions , antigen presenting cells, take up antigen and present it in an immunogenic form to T - helper cells and to B cells .

TREM-triggering receptor exposed on myeloid cells 1(TREM-1) is a cell surface receptors of the immunoglobulin superfamily, involved in the innate inflammatory response to bacterial and fungal infections. TREM-1 activation and expression occur synergistically with TLR as the TREM family contains both inhibitory and activating receptors capable of TLRs moreover , TREM -1 has also been associated with NOD-like receptors (NLR), responsible for sensing microbial danger and amplifying the inflammatory response. [10]

The synergism of activation between TREM-1 and TLRs (Toll Like Receptors) leads to an amplification loop of the NF-κB pathway.

significant in accordance with increasing severity of disease. Disease activity in periodontal disease may range from slow, chronic, progressive destruction to brief and acute episodic bursts with varying intensity and duration.

The periodontal pathogens are as follows Porphyromonas gingivalis -This bacterium, previously known as Bacteroides gingivalis, is a strictly anaerobic, Gram negative rod. It is black-pigmented microorganism which produces a black pigment. Many virulence mechanisms have been identified. P.g expresses three major virulence factors-fimbriae, gingipains and lipopolysaccharides. P.g is a one of the major periodontopathogenic with the ability to adhere , and to invade oral epithelia in vitro.

The composition of the subgingival microbial flora and the level of pathogenic species differ from subject to subject as well as from site to site. The currently recognized key Gram negative periodontopathogens include: Porphyromonas gingivalis (P.g), Prevotella intermedia (P.i), Bacteroides forsythus (B.f), Aggregatibacter actinomycetemcomitans (A.a), Fusobacterium nucleatum (F.n), Capnocytophaga species (C.sp), Campylobacter rectus (C.r).[7] Also, the following bacteria could be isolated: Eubacterium spp, Peptostreptococcus micros, Selenomonas spp, Spirochaetes.A correlation was found between P.g, P.i, C.r, Eikenella corrodens, Selenomonas sp, Bacteroides species, Spirochetes and adult or refractory periodontal disease.[8]

The microorganisms could produce disease directly, by invasion on the tissues, or indirectly by bacterial enzymes and toxins. In order to be a periodontal pathogen, a microorganism must have the following:

• the organism must occur at higher numbers in disease-active sites than at disease-inactive sites
• elimination of the organism should arrest disease progression
• the organism should possess virulence factors relevant to the disease process
• the organism should elicit a humoral or cellular immune response
• animal pathogenicity testing should infer disease potential. [9]

The periodontal pathogens are as follows Porphyromonas gingivalis -This bacterium, previously known as Bacteroides gingivalis, is a strictly anaerobic, Gram negative rod. It is black-pigmented microorganism which produces a black pigment. Many virulence mechanisms have been identified. P.g expresses three major virulence factors-fimbriae, gingipains and lipopolysaccharides. P.g is a one of the major periodontopathogenic with the ability to adhere , and to invade oral epithelia in vitro.

This article is distributed under the terms of the Creative Commons Attribution-Non Commercial 4.0 International License. ©2021 Muslim OT et al.
activation resulting in an increase in the production of pro-inflammatory cytokines such as IL-1Beta and TNF-alpha as well as inhibition of IL-10 production.[11] On the molecular level, TREM-1 regulates immune cell function, by forming an intracellular complex with signaling adapter DNAx activating lprotein of 12FDa(DAP12), is involved in immune response to bacterial and fungal infections. Particularly by amplifying the production of pro-inflammatory cytokines by the host.

Monocytes are a major source of TREM-1 in inflammation. It’s expression is regulated during the course of bacterial and fungal infections. Individual microbial components can cause up regulation of cell surface TREM-1 by monocytes, as well as its release in the soluble(s) TREM-1 form. Release of TREM-1 may constitute a marker of systemic sepsis, septic arthritis, pneumonia. It has recently been demonstrated that P.gingivalis induces TREM-1 gene expression in monocytes, which is then released from their cell surface as TREM-1. Modulation of cytokines production is an important concept in the treatment of various inflammatory diseases.

sTREM-1, the soluble form of TREM-1 resulting from the cleavage by MMP (Matrix Metalloproteinase) of the extracellular portion of this receptor. [12] Higher concentrations of sTREM-1 were noted in gingival crevicular fluid (GCF) and saliva from patients with periodontitis. TREM-1 was also detected in the gingival tissues of patients with periodontitis, its tissue expression being correlated with the presence of red complex bacteria. [13]

sTREM-1 could potentially have a prognostic role in the outcome / healing of periodontal lesions after non-surgical treatment, as described above for other diseases. In order to better understand the role of sTREM-1 in the inflammatory processes of periodontal disease, it could therefore be interesting to evaluate this molecule in response to periodontal treatment, which has not yet been studied. Moreover, the progression of periodontitis is also modified by local, systemic or environmental factors. Smoking, quality and quantity of saliva, drugs or psychological stress are risk factors. Stress markers, such as glucocorticoids, can disturb the metabolism of fats, proteins and glucose, (2) have an immunosuppressive action as glucocorticoid receptors are present on macrophages, granulocytes, lymphocytes and (3) could modulate microbiota. [14] Activation of TREM-1 by periodontal bacteria, upstream of overexpression of pro-inflammatory cytokines by immune cells, could be modified in the presence of psychological factors (stress/anxiety). sTREM-1, reflecting activation of the membrane receptor, could be analyzed to assess this possible impact.

TREM-1 (sTREM-1) can be found in increased amounts in the saliva and serum of patients with periodontitis, when compared to healthy individuals. Furthermore, it has been shown that the amount of sTREM-1 in gingival cervical fluid from sites affected by chronic aggressive periodontitis is correlated with the presence of the ‘red complex’ bacteria, as well as the clinical measurements of the disease. It is not yet clear if these correlations of TREM-1 with clinical and microbiological parameters can also be found at the molecular level, within the inflamed periodontal tissues. Our team has extensive knowledge and research experience that has translated into high quality publications. [15–24] The aim of this systematic review is to evaluate the role of Triggered Receptor Expressed in Myeloid Cells 1(TREM -1) TREM in periodontal disease.

**Structured Questions**

1. Whether there is a correlation between the TREM and severity of periodontal disease?
2. What is the influence of TREM on inflammatory mediators in periodontal tissues?
3. Is TREM level elevated in periodontal disease state compared to periodontal health whether its level differs with disease severity?
4. What are the factors influencing TREM expression in periodontal disease?
5. What is the influence of TREM on inflammatory mediators in periodontal tissues?
Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease - A Systematic Review

**Aim**
The aim of this systematic review is to evaluate the role of Triggered Receptor Expressed in Myeloid Cells 1 (TREM-1) TREM in periodontal disease.

**MATERIALS AND METHODS**

**Source Used And Search Methodology**
A comprehensive literature search of the following databases were done which included studies of the Pubmed, Pubmed central, Medline, Cochrane database of systematic reviews, Mesh, Science direct, Embase databases up till the month of March 2021. The search was performed using key words and terms mentioned in Table. No limits and language restriction were applied during the electronic search to include all the possible clinical trials in the potential relevant article search phase of the systematic review. No time restriction was applied. The search was completed by checking the reference terms and also the key words given in the relevant articles. A manual hand search was also carried out. The articles were screened on the basis of title and abstract. Full text was then downloaded for the relevant articles which fulfilled the inclusion criteria mentioned.

**Pico Analysis**

**POPULATION** - Patient with periodontal disease

**INTERVENTION:** NOT APPLICABLE

**COMPARISON** - correlation between TREM and periodontal disease

**OUTCOME** - TREM levels

**Inclusion Criteria**
1) Articles reporting randomised controlled trials of TREM in periodontal disease.
2) Studies involving clinical trials of TREM in periodontal disease.
3) Randomized controlled clinical trials which assessed the TREM levels and Periodontal disease.
4) Cross sectional and longitudinal studies which associated TREM levels and different types of periodontal diseases.
5) Studies which correlated the influence of periodontal pathogens and TREM levels.
6) Studies which assessed the influence of TREM in host immune response.

**Exclusion Criteria**
1) Review articles
2) Animal studies
3) Not relevant
4) Abstract not present
5) No intervention of TREM
6) Studies with no appropriate statistical data
7) Case reports
8) Case series

**Sources of Electronic Search**
- Pubmed
- Pubmed Central
- MEDLINE, US National Library of Medicine
- Science Direct
- Google Scholar
- Cochrane database

**Sources of Hand Search**
- Journal of Periodontology
- Journal of Clinical Periodontology
- Journal of Periodontal Research
- Journal of Indian Society of Periodontology
- Infection and Immunity

**Search Through Pubmed**

((((((((("Periodontitis"[Mesh]) OR "Chronic Periodontitis"[Mesh]) OR "Aggressive Periodontitis"[Mesh]) OR "Periapical Periodontitis"[Mesh]) OR "Periodontal Diseases"[Majr]) OR "Gingival Diseases"[Majr]) OR "Gingivitis"[Mesh]) AND "TREM1 protein, human" [Supplementary Concept]) OR "TREM1 protein, human" [Supplementary Concept]) OR "TREM-2a receptor" [Supplementary Concept]) OR "TREM-2b receptor" [Supplementary Concept]) OR "Receptors, Pattern Recognition"[Majr] OR "Triggering Receptor Expressed on Myeloid Cells-1"[Mesh]
Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease: A Systematic Review

J Popul Ther Clin Pharmacol Vol 30(10):e125–e146; 08 May 2023. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License. ©2021 Muslim OT et al.
Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease: A Systematic Review

J Popul Ther Clin Pharmacol Vol 30(10):e125–e146; 08 May 2023. This article is distributed under the terms of the Creative Commons Attribution-Non Commercial 4.0 International License. ©2021 Muslim OT et al.
Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease - A Systematic Review

Electronic Search Strategy For Google Scholar

Electronic Search Strategy For Cochrane Library

Advanced Search

J Popul Ther Clin Pharmacol Vol 30(10):e125–e146; 08 May 2023. This article is distributed under the terms of the Creative Commons Attribution-Non Commercial 4.0 International License. ©2021 Muslim OT et al.
Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease - A Systematic Review

Electronic Search Strategy For Science Direct

Electronic Search Strategy For Pubmed Central

Electronic Search Strategy For Pubmed
RESULTS
The electronic databases and hand search yielded a total of 559 articles. 89 full text articles after removal of duplicated articles. 78 articles are excluded and 11 articles are included in this study. Full texts for 11 articles were produced and Data extraction was done. A description of each study is given in the tables.

The final 11 studies included in that 6 in vitro study, 4 cross sectional study, 1 case control study .11 articles found relevant according to the inclusion criteria. 11 studies discussed the role of TREM levels in periodontal disease. Among 11 studies, 5 studies discussed about sTREM-1 levels and IL levels against periodontal pathogens. 1 study discussed Active Matrix Metalloproteinase (aMMP-8) predicts TREM-1 in saliva. 1 study discussed PGLYRP1 and TREM-1, IL-beta levels in gingival inflammation. 1 study discussed TREM-1, PGLYRP1, MMP-8 in peri implant disease. 1 study discussed TREM-1 response in periodontium in elderly population.1 study discussed TREM-1, mRNA expression in MM6 cells( mono mac ).1 study discussed TREM-1, TREM-2 in inflamed human gingiva.

TABLE 2: Characteristics And Summary Of Included Studies

<table>
<thead>
<tr>
<th>Article</th>
<th>Author Journal</th>
<th>Study Design</th>
<th>Materials And Groups</th>
<th>Statistical Analysis</th>
<th>Result</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involvement of the TREM-1/</td>
<td>Georgio and N.Belibasakis and</td>
<td>In Vitro study</td>
<td>P.gingivalis and strain W50 grown</td>
<td>ANOVA Bonferroni</td>
<td>Synthetic TREM-1 antagonist</td>
<td>It is not clear if the up regulation of</td>
</tr>
</tbody>
</table>
### Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease: A Systematic Review

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Journal</th>
<th>Authors</th>
<th>Materials and Groups</th>
<th>Statistical Analysis</th>
<th>Result</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation of the TREM-1 pathway in human monocyte by periodontal pathogens and oral commensal bacteria</td>
<td>Mrudala varant, Elaine M, Hasse, Jason G. Kay, Frank A. Scannapieco</td>
<td>In Vitro study</td>
<td>Human Monocyte cell like cell line THP-1 Cells were maintained in RPMI Glutamax medium supplemented with 10% FBS At a density of 1-2 x 10⁶ cell/ml</td>
<td>One way Analysis, Tukey HSD Post hoc test, Bonferroni Test</td>
<td>Synthetic TREM-1 antagonist LP17 reduces the P. gingivalis induced IL-1 Beta ; IL-6 Secretion by approximate 1 y 50% $P&lt;0.05$</td>
<td>Further studies are needed to investigate strategies to prevent or diminish inflammation and periodontal disease activity.</td>
</tr>
</tbody>
</table>

### DAP 12 and pathway in the innate immune response to Porphyromonas gingivalis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal</th>
<th>Year</th>
<th>Study Design</th>
<th>Materials and Groups</th>
<th>Statistical Analysis</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>N.Bostanci et al. Thomas Thornhearn</td>
<td>Journal of molecular Immunology</td>
<td>2011</td>
<td>In Vitro study</td>
<td>Alanobically on Columbia Bhor Ag (CBA) plates for 3-4 days at 37°C followed by sub culturing 2-3 days at 370°C in brain heart fusion (Broth)</td>
<td>Post Hoc test, Bonferroni Test</td>
<td>LP17 reduces the P. gingivalis induced IL-1 Beta ; IL-6 Secretion by approximate 1 y 50% $P&lt;0.05$</td>
</tr>
<tr>
<td>Article</td>
<td>Author Journal</td>
<td>Study Design</td>
<td>Materials And Groups</td>
<td>Statistiscal Analysis</td>
<td>Result</td>
<td>Limitation</td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
<td>--------------</td>
<td>----------------------</td>
<td>----------------------</td>
<td>--------</td>
<td>------------</td>
</tr>
<tr>
<td>Porphyromonas gingivalis regulates TREM-1 in Human polymorphonuclear neutrophils via its gingipains</td>
<td>Nagihan Bosatnci, Thomas Thumhear</td>
<td>In Vitro study</td>
<td>P. gingivalis wild type W50 strain and gingipain knock-out mutant K1A and E8 strain were used. All 3 strains were grown anaerobically on Columbia Blood agar plates for 3-4 days at 37°C in brain heart infusion broth containing 0.5% hemin and 0.2% menadione</td>
<td>One way Analysis (ANOVA) Bonferroni Post hoc test</td>
<td>Engagement of TREM-1 means of anti TREM-1 antibodies, enhanced the capacity of P. gingivalis to stimulate IL-8 production. Conversely antagonism of TREM-1 using a synthetic peptide resulted in reduction of IL-8 secretion. P. gingivalis mutant strains, we identified the Arg- gingipain to be responsible for shedding of sTREM-1 from PMN surface. Lys gingipain had the capacity to degrade TREM-1.</td>
<td>Only 3 strains were used in this study. P. gingivalis wild strain and gingipain knock out mutant K1A and E8 strain is deficient in both Lys Gingipain. Further studies are needed to include more strains, for better outcome.</td>
</tr>
</tbody>
</table>

**METHOD:**
Cytotoxicity Assay, RNA Extraction, cDNA synthesis, PCR ELISA Flow cytometry analysis confocal

**VARIABLES ASSESSED:**
P. gingivalis W50 strain gingipain knock-out mutant K1A and E8 strain
### Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease - A Systematic Review

**Article** | **Author Journal** | **Study Design** | **Materials And Groups** | **Statistical Analysis** | **Result** | **Limitation**
---|---|---|---|---|---|---
Regulation of PGLYRP1 and TREM-1 during progression and resolution of gingival inflammation. | A.silbereisen, A.K.Hallam G.G.Nascimento T.Sorsa, G.N.Belibask, R.Lopez, N.Bostanci | In Vitro study | Study (n= 42) subjects, mean age : 23.8 ± 3.7 y comprised a recruitment step (day -14) followed by experimentally induced biofilm formation. (Induction [1] phase, day 0 to + 21) and and 2-weeks Resolution (R) Phase (day +21 to +35) Plaque was recorded by Modified Quigley and Hein Plaque Index | SEM | Engagement of TREM-1 means of anti TREM-1 antibodies, enhanced the capacity of P.gingivalis to stimulate IL-8 production. Conversely antagonism of TREM-1 using a synthetic peptide resulted in reduction of IL-8 secretion. P.gingivalis mutant strains, we identified the Arg-gingipain to be responsible for shedding of sTREM-1 from PMN surface. Lys - gingipain had the capacity to degrade TREM-1. | Only 3 strains were used in this study. P.gingivalis wild strain and gingipain knock out mutant K1 A and E8 strain is deficient in both Lys Gingipain. Further studies are needed to include more strains, for better outcome. 

#### Expression and regulation of triggering

**Article** | **Author Journal** | **Study Design** | **Materials And Groups** | **Statistical Analysis** | **Result** | **Limitation**
---|---|---|---|---|---|---
Expression and regulation of triggering | Clinical and Experimental Immunology | In Vitro study | Study (n= 45) subjects, | Graph pad software version 6.02 IBM, SPSS | Gingival tissue TREM-1 expression | Further research is necessary to identify the...
<table>
<thead>
<tr>
<th>Article</th>
<th>Author Journal</th>
<th>Study Design</th>
<th>Materials And Groups</th>
<th>Statistical Analysis</th>
<th>Result</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased expression of triggering receptors expressed on myeloid cells 1 &amp; 2 in inflamed human gingiva.</td>
<td>Journal of periodontal research S.S.Chen, K. Wang, J.Zahoor, W.C.Wu, Y.F.Wu, L.Zahoor.</td>
<td>Cross section study</td>
<td>Healthy Individual-31 (19males;12 females) (PD&lt;3mm) Chronic periodontitis=5 3 (26 males;27 females)</td>
<td>Unpaired two - tailed student's T test Non parametric Mann whitney U test Spearman's rank correlation coefficient.</td>
<td>TREM-1, TREM-2 were also found expressed in gingival epithelial cells. TREM-1 was detected</td>
<td>TREM-1, TREM-2 roles in the immune response during periodontitis, but the mechanisms that contribute to their expression</td>
</tr>
</tbody>
</table>
Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease - A Systematic Review

**METHOD:**
- Quantitative Immunohistochemical Analysis.
- Quantitative real time polymerase chain reaction.

**VARIABLE ASSESSED:**
- TREM-1
- TREM-2

Bonferron

In almost all gingival epithelium from both healthy and inflamed biopsy.

Expression levels of TREM-1,2 were significantly increased in periodontitis group compared to healthy group.

Patterns during the progress of periodontitis remain unclear. Hence further studies are needed to investigate.

<table>
<thead>
<tr>
<th>Article</th>
<th>Author Journal</th>
<th>Study Design</th>
<th>Materials And Groups</th>
<th>Statistical Analysis</th>
<th>Result</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The modulation of the TREM-1/PGLYRP1/MMP-8 axis in peri-implant disease</td>
<td>Clinical Oral Investigation Mayla K.S. Teixeira, Ronald Lira-Junior, Eduardo Jose Veras Lourenco, Daniel Morales Telles, Elisabeth A. Bostrom, Carlos Marcelo Figueredo, Nagihan Bostanci. 2019</td>
<td>Cross sectional study</td>
<td>Participants - 77 Healthy - 29 Gingivitis - 18 Periodontitis - 16 Mucositis - 20 GINGIVITIS GROUP: Bleeding on probing more than 20% PD&lt;3mm CAL&lt;1mm PERIODONTITIS GROUP: Bleeding on probing more than 30% PD&lt;5mm CAL&gt;3mm MATERIALS AND METHODS: Study includes 77 patients (29</td>
<td>SPSS version 24 Shapiro Wilk test Mann Whitney test Chi square test Spearman correlation coefficient</td>
<td>Bonferron</td>
<td>It’s cross-sectiona l nature does not allow any causal claim to be made. Also, the similarities in marker levels in the four groups may be temporal in nature. Prospective studies with larger cohorts would clarify the relationship between the levels of TREM-1/PGLYRP1/MMP-8 axis in peri-implant disease. It is also important to point out that</td>
</tr>
</tbody>
</table>
Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease

A Systematic Review

This article is distributed under the terms of the Creative Commons Attribution-Non Commercial 4.0 International License. ©2021 Muslim OT et al.

males and 48 females; mean age55.0+11.5). 18 having periodontitis , 20 having mucositis and 23 having peri-implant it is.Patients were clinically examined and unstimulated whole saliva was collected.

showed significantly higher levels of PGLYRP1, MMP-8 and MMP-8/TIMP-1 ratio than patients with PD<6mm the differences presented in the clinical parameters section are related to inclusion criteria rather than any relevant clinical findings.

<table>
<thead>
<tr>
<th>Article</th>
<th>Author</th>
<th>Study Design</th>
<th>Materials And Groups</th>
<th>Statistical Analysis</th>
<th>Result</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline inhibits TREM-1 induction by Porphyromonas gingivalis</td>
<td>Nagihan Bostanci, Georgios N. Belibasakis</td>
<td>Invitro study</td>
<td>Porphyromonas gingivalis strain W50 (OMZ 308) Was grown anaerobically on Columbia blood agar (CBA) plates for 3-4 days at 37 degree centigrade, followed by anaerobic subculturing for 2-3 days at 3 degree centigrade in brain heart infusion broth.</td>
<td>ANOVA Bonferroni post hoc test.</td>
<td>Porphyromonas gingivalis enhanced sTREM-1 release after 4hr and 24hr . SDD( sub anti microbial doses of doxycycline ) inhibited sTREM-1 release by cells, after 4hr of administrati on. SDD indeed inhibited P.gingivalis induced IL-8 secretion in a dose dependent manner.</td>
<td>It was recently demonstrated that P. gingivalis regulates the TREM-1/DA P12 signaling pathway in monocytic cells, in a manner that amplifies pro-inflammatory responses to this pathogen. However, it is not known if this pathway can be inhibited by SDD, which could shed light to the generalized anti-inflammatory effects of SDD in periodontal treatment. Hence further studies are</td>
</tr>
</tbody>
</table>
### Article

**Impact of aging on TREM-1 responses in the periodontium: a cross-sectional study in an elderly population.**

**Veli ozgen oztuk, Georgios N.Belibasakis, Gulnur Emingil and Nagihan Bostanci**

**Journal of clinical periodontology** 2017

<table>
<thead>
<tr>
<th>Article Title</th>
<th>Author Journal</th>
<th>Study Design</th>
<th>Materials And Groups</th>
<th>Statistical Analysis</th>
<th>Result</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Impact of aging on TREM-1 responses in the periodontium: a cross-sectional study in an elderly population.</strong></td>
<td>Veli ozgen oztuk, Georgios N.Belibasakis, Gulnur Emingil and Nagihan Bostanci</td>
<td>Cross sectional study</td>
<td>Healthy patients n=51 Periodontal disease n=17 Gingivitis n=19 Patients with chronic periodontitis n=15</td>
<td>Graph pad software Kruskal-Wallis one-way ANOVA and Dunn's test. Bonferroni</td>
<td>GCF Volume, total protein concentrations, and sTERM-1 levels in GCF were similar among the groups (p&gt;0.05). Significantly higher T.forsythia levels were observed in subgingival plaque samples harvested from patients with gingivitis and CP, than in those from healthy patients participants (p&lt;0.05). However, the subgingival levels of other four periodontal pathogens and total bacteria (p&lt;0.05).</td>
<td>This study does not allow for the continuous monitoring of the studied inflammatory mediators over time. Future studies could address a similar question on sTERM-1 in a prospective manner, monitoring patients of different ages and over periods of time.</td>
</tr>
</tbody>
</table>
### Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease - A Systematic Review

**J Popul Ther Clin Pharmacol Vol 30(10):e125–e146; 08 May 2023.**

This article is distributed under the terms of the Creative Commons Attribution-Non Commercial 4.0 International License. ©2021 Muslim OT et al.

<table>
<thead>
<tr>
<th>Article</th>
<th>Author Journal</th>
<th>Study Design</th>
<th>Materials And Groups</th>
<th>Statistical Analysis</th>
<th>Result</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparison of sTREM-1 and associated periodontal and bacterial factors before/after periodontal therapy and impact of psychosocial factors</td>
<td>M. Dubar, J.P. Frippiat, T. Remen, G. Gibot, B. Bisson</td>
<td>Journal of clinical periodontology</td>
<td>Periodontitis subjects n=30 Control group n=30 GCF and saliva samples were collected. Each patient filled in stress and anxiety self assessment questionnaires and provided saliva samples. METHOD: qPCR ELISA</td>
<td>Mann whitney test Mac namara test Wilcoxon test Pearson's coefficient correlation Multivariable stepwise logistic regression SAS version 9.4</td>
<td>After SRP cervicular sTREM-1 levels decreased p&lt;0.001 and were linked to a PPD decrease but remained higher in pathological than in healthy sites p&lt;0.001. Higher sTREM-1 levels were associated with P.gingivalis, T.denticola, C.rectus in pathological sites after SRP p&lt;0.05</td>
<td>Further studies are needed to include the most severely affected subjects both at periodontal stage 3 and 4 and stress or anxiety level could help in clarify the role of psychological factors in etiopathogenesis is of this disease.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Article</th>
<th>Author Journal</th>
<th>Study Design</th>
<th>Materials And Groups</th>
<th>Statistical Analysis</th>
<th>Result</th>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Point-Of-Care Test of Active Matrix Metalloprote inase -8 (Amp-8) Predicts Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1) Levels In Saliva</td>
<td>Ismo T. Raisanen, Anna Maria Heikkinen, Elinira Pakbazneja D Esmaeili, Taina Tervahartiala, Riitta Pajukanta, Anjelika Silbereisen, Nagihan Bostanci And Timo Sorsa</td>
<td>Case control study</td>
<td>Subjects n=47, aged 15-17, were tested with aMMP-8 Poc test, which was followed by full mouth clinical examination of the assessment of periodontal, mucosal, and oral health. Method- aMMP-8 Poc test</td>
<td>Spearman rank correlation Shapiro-Wilk test Mann-Whitney U test aMMP-8 Poc test Bonferroni correlation Bonferron</td>
<td>The number of periodontal pockets with ≥4mm was significantly lower among the adolescent s with a negative aMMP-8 PoC test result and TREM-1 levels below 75 pg/mL (P&lt;0.05). In</td>
<td>Sample size is small Results are not definitive More research with other populations and larger sample sizes are needed to confirm our results.</td>
</tr>
</tbody>
</table>
Periodontitis is a chronic inflammatory disease that affects the supporting structures of the teeth and is considered as one of the most common reasons for tooth loss. Periodontal disease could be defined as a disorder of supporting structures of teeth, including the gingiva, periodontal ligament and alveolar bone. Periodontal disease develops from a pre-existing gingivitis. However, not every case of gingivitis develops into a periodontal disease. The inflammation of gingiva alone is termed gingivitis, and the severe inflammation of the periodontal ligament with destruction of alveolar bone is called periodontal disease.

TREM-triggering receptor exposed on myeloid cells 1(TREM-1) is a cell surface receptor of the immunoglobulin superfamily, involved in the innate inflammatory response to bacterial and fungal infections. TREM-1 activation and expression occur synergistically with TLR as the TREM family contains both inhibitory and activating receptors capable of TLRs moreover , TREM -1 has also been associated with NOD-like receptors (NLR), responsible for sensing microbial danger and amplifying the inflammatory response.

The synergism of activation between TREM-1 and TLRs (Toll Like Receptors) leads to an
amplification loop of the NF-kB pathway activation resulting in an increase in the production of pro-inflammatory cytokines such as IL-1Beta and TNF- alpha as well as inhibition of IL-10 production . On the molecular level, TREM-1 regulates immune cell function, by forming an intracellular complex with signaling adapter DNAX activating protein of 12FDa(DAP12), which is involved in immune response to bacterial and fungal infections. Particularly by amplifying the production of pro-inflammatory cytokines by the host.

Bostanci.et.al, [25] showed that synthetic TREM-1 antagonist LP17 reduced the P. gingivalis induced IL-1Beta, and IL-6 secretion by approximately 50%. Potentiate the pro-inflammatory responses to P. gingivalis infection. P. gingivalis can stimulate the expression of the TREM-1/DAP12 pathway in monocytic cells, associated with an increased release of stREM-1, which may constitute a marker of systemic inflammation.

Bostanci.et.al, [26] showed that antagonism of TREM-1 using synthetic peptide resulted in reduction of IL-8 secretion .using isogenic P.gingivalis mutant strain ,Arg- gingipain to be responsible for Shedding of sTREM -1 from the PMN surface, whereas the Lys- gingipain had the capacity to degrade TREM-1. P. gingivalis may employ its Lys-tingipain to control this and remain stealth. Hence, dual regulation of stREM-1 release and degradation by two different gingipains may be a novel mechanism by which P. gingivalis evades the host defenses and establishes chronic periodontal inflammation.

Bostanci et.al, [27] SDD inhibits bacterially induced TREM-1, and this effect may partly account for its generalized anti-inflammatory properties. SDD as an adjunct treatment for periodontal disease. SDD could serve as a suitable modulator of systemic inflammatory responses. Varant .et.al, [28] showed that commensal and pathogenic oral bacteria activate the TREM-1 pathway, resulting in a pro-inflammatory TREM-1 activity dependent increase in proinflammatory cytokine production.Activation of TREM-1 also resulted in increased production of proinflammatory cytokines by the monocytic cells, as they were significantly reduced when the cells were treated with TREM-1 inhibitor. The increase in cytokines is consistent with earlier reports that stimulation of TREM-1 can result in synergistic upregulation of signaling initiated by other pattern recognition receptors such as the TLRs.

Willi.et.al, [29] showed that biofilm challenged MM6 cells exhibited higher TREM-1 expression. Engagement or inhibition of TREM-1 affected the capacity of the biofilm to stimulate interleukin(IL)-1BETA , but not IL-8, secretion by the cells.Chen.et.al, [30] show that TREM-1and TREM-2 were also found expressed in gingival epithelial cells. TREM-1 andTREM-2 were significantly increased in the periodontitis group compared to the healthy group.The increased expression of TREM-1 and TREM-2 levels in periodontitis may confer diagnostic and potential therapeutic targets as well as indicating their association with the clinical severity of the disease.

Teixeira.et.al,[31] Patients with PD>6mm showed significantly higher levels of PGLYRP1,MMP-8 and MMP-8/TIMP -1 ratio than patients with PD<6mm. The levels of TIMP-1 were significantly higher in patients with peri-implantitis compared to patients with periodontitis. Marie.et.al , [63] showed that higher TREM-1 Were associated with P.gingivalis. T. denticola, C. rectus, in pathological sites after SRP. (P<0.05).This study presents the first evaluation of stREM-1 levels after SRP.

Ismo.et.al, [32] showed that adolescents with a positive aMMP- 8 PoC test result together with elevated TREM-1 levels had significantly higher number of periodontal pockets with>4mm(p<0.001). He found a significant association between the aMMP-8 PoC test result and the concentrations of TREM-1 and aMMP-8.

This systematic review included in vitro study, case control study, cross sectional study indicates the role of TREM In periodontal disease. The current evidence and results prove that further in the field of TREM could throw a light into the understanding of the inflammatory process of periodontal disease. From the systematic review
it is evident that TREM levels are increased in periodontal disease, against periodontal pathogens. Synthetic TREM-1 blockade could mitigate the host inflammatory response and be useful as an adjunct therapy for the treatment of periodontal disease. Further studies are needed to show the specific role of sTERM-1 in inflammatory conditions and diagnostic tests will be available for clinical use in dental practices to assist in patient care. TREM-1 modulation to provide therapeutic effects and arrest the tissue destruction common in periodontitis.

CONCLUSION
The current evidence and results prove that TREM has a significant role in modifying the inflammatory process of periodontal disease. From this systematic review it is evident that TREM levels are increased in periodontal disease, increase in TREM levels correlate with increase in levels of periodontal pathogens. Synthetic TREM-1 blockade could mitigate the host inflammatory response and be useful as an adjunct therapy for the treatment of periodontal disease. Further studies are needed to show the specific role of sTERM-1 in inflammatory conditions and diagnostic tests will be available for clinical use in dental practices to assist in patient care. TREM-1 modulation would provide therapeutic effects and arrest the tissue destruction caused in periodontitis.

REFERENCES
Role of Triggered Receptor Expressed in Myeloid Cells (TREM) in Periodontal Disease - A Systematic Review


