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

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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

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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 keystone 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 socransk. [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 micro-organisms
(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

significantly 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 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 is 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. Aggregatibacter actinomycetemcomitans A.a., previously Actinobacillus actinomycetemcomitans, is a Gram negative facultative non motile coccoid 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-kB pathway

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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- inflammation 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 STREM-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,(1)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. Gene expression 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 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?

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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 "TREML1 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]

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Advanced search in Pubmed

#13 Search: ((((((((((("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 "TREML1 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] NOT "TLR" Filters: Free full text, Full text, Clinical Trial, Randomized Controlled Trial

#12 Search: ((((((((((("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 "TREML1 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] NOT "TLR" Filters: Full text, Clinical Trial, Randomized Controlled Trial

#11 Search: ((((((((((("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 "TREML1 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] NOT "TLR" Filters: Clinical Trial, Randomized Controlled Trial

#10 Search: ((((((((((("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 "TREML1 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] NOT "TLR" Filters: Free full text, Clinical Trial, MetaAnalysis, Randomized Controlled Trial

#9 Search: ((((((((((("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 "TREML1 protein

#8 Search: ((((((((((("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 "TREML1 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] NOT "TLR" Filters: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review

#7 Search: ((((((((((("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 "TREML1 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] NOT "TLR" Filters: Clinical Trial, Randomized Controlled Trial, Systematic Review

#6 Search: ((((((((((("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 "TREML1 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] NOT "TLR" Filters: Free full text, Clinical Trial, Randomized Controlled Trial, Systematic Review

#5 Search: ((((((((((("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 "TREML1 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] NOT "TLR" Filters: Free full text, Clinical Trial, Randomized Controlled Trial

#4 Search: ((((((((((("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 "TREML1 protein

#3 Search: ((((((((((("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 "TREML1 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] NOT TLR filters

#2 Search: ((((((((((("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 "TREML1 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] NOT "TLR"

#1 Search: ((((((((((("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 "TREML1 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] Sort by: Most Recent

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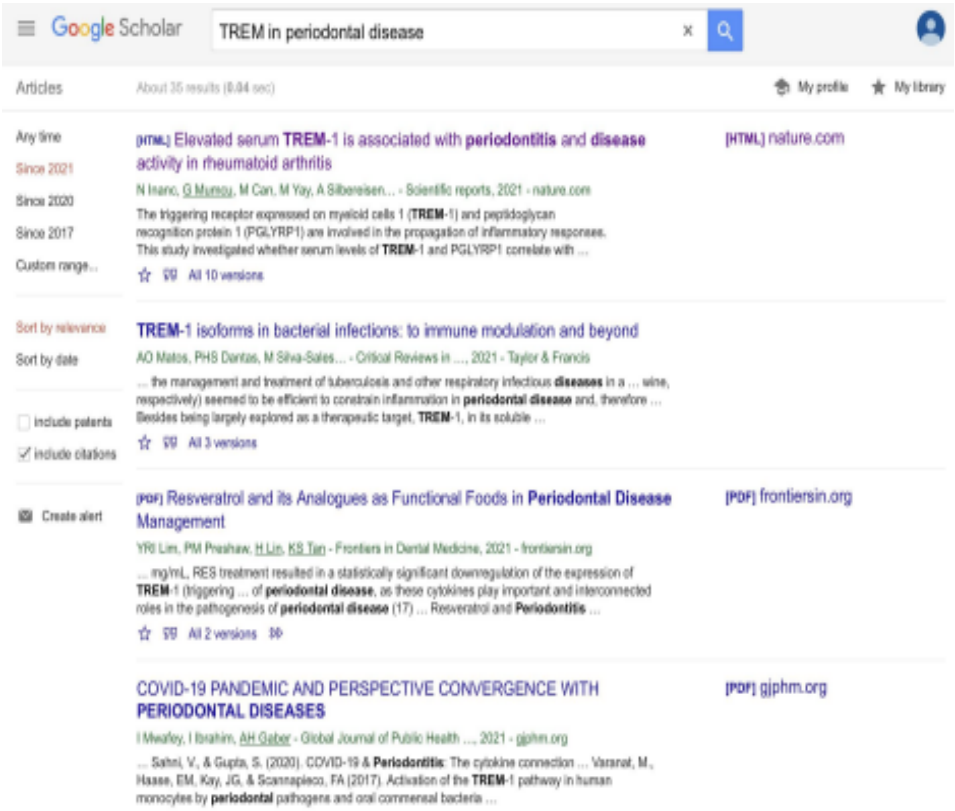
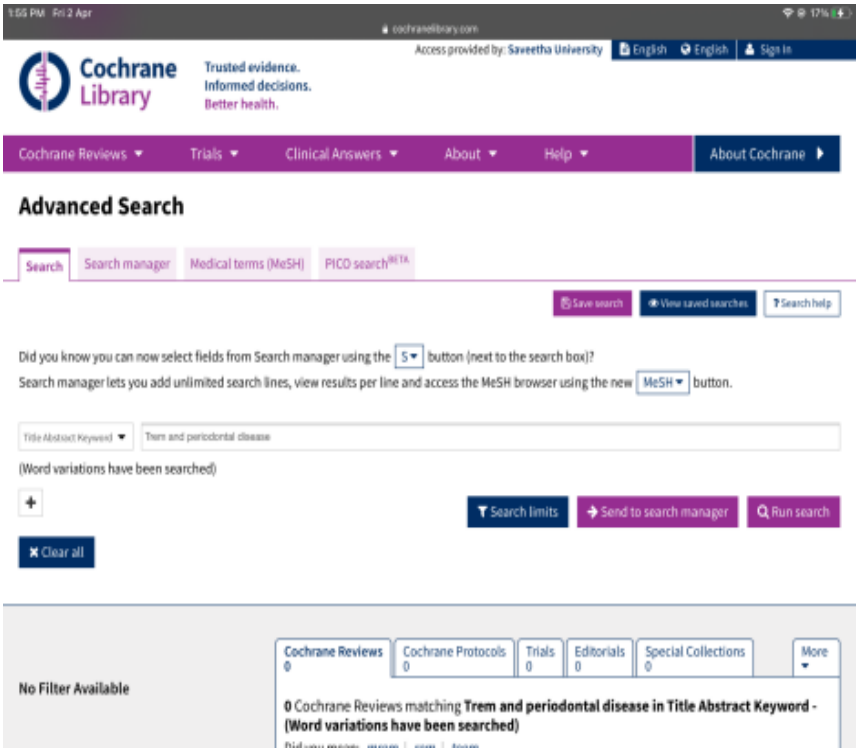
Electronic Search Strategy For Google Scholar



Electronic Search Strategy For Cochrane Library



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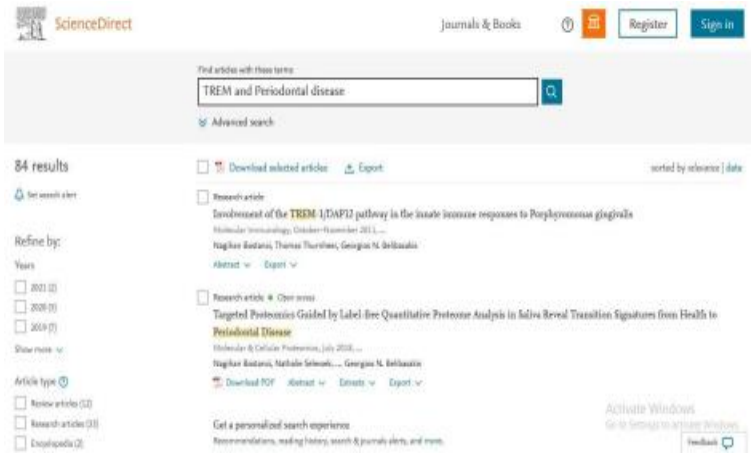
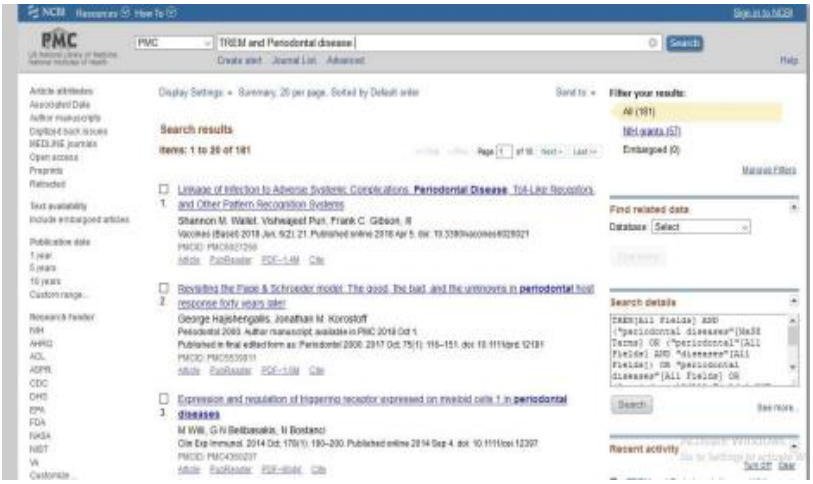
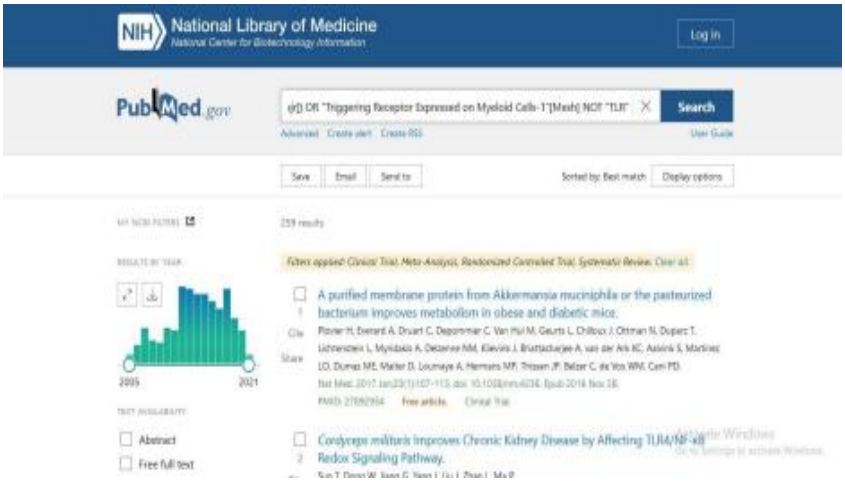
Electronic Search Strategy For Science Direct



Electronic Search Strategy For Pubmed Central



Electronic Search Strategy For Pubmed



Search Strategy Flow Chart

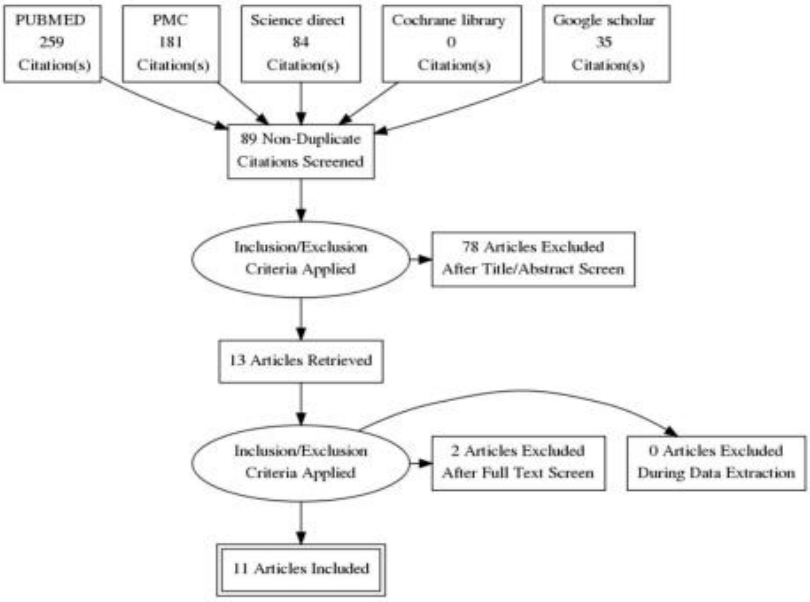


Chart 1

TABLE 1: Excluded Studies

S.No	Author, Citation Reason For Exclusion
1.	Rudick.et.al (Review article)
2.	Bostanci .et.al (Animal study)

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. 1study 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

Article	Author Journal	Study Design	Materials And Groups	Statistical Analysis	Result	Limitation
Involvement of the TREM-1/	Georgio and N.Belibasakis and	In Vitro study	P.gingivalis and strain W50 grown	ANOVA Bonferroni	Synthetic TREM-1 antagonist	It is not clear if the up regulation of

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DAP 12 and pathway in the innate immune response to Porphyromonas gingivalis.	N.Bostanci et.al. Thomas Thurnhear Journal of molecular Immunology 2011		anaerobically on Columbia Bhor Ag (CBA) plates for 3-4 days at 370C followed by sub culturing 2-3 days at 370C in brain heart fusion (Broth) METHOD: Bacterial viability assay, Cytotoxicity assay, qPCR, Confocal laser scanning VARIABLES ASSESSED: TREM-1 DAP-12	Post Hoc test Bonferron	LP17 reduces the P.gingivalis induced IL-1 Beta ;IL-6 Secretion by approximate l y 50% P<0.05	TREM-1 in combination with a steady DAP12 expression is adequate to enhance downstream signalling for the amplification of Inflammatory response.

Article	Author Journal	Study Design	Materials And Groups	Stastisical Analysis	Result	Limitation
Activation of the TREM-1 pathway inhuman monocyte by periodontal pathogens and oral commensal bacteria	Mrudala varant, Elaine M, Hasse, JasonG. Kay, Frank A. Scannapieco 2016	In Vitro study	Human Monocyte cell like cell line THP-1 Cells were maintained in RPM1 Glutamax medium supplemented with 10% FBS At a density of 1-2 x 10cell/ml METHOD: Bacterial viability assay, Cytotoxicity assay, qPCR, Confocal laser scanning VARIABLES	One way Analysis Tukey HSD Post hoc test Bonferron	Synthetic TREM-1 antagonist LP17 reduces the P.gingivalis induced IL-1 Beta ; IL-6 Secretion by approximate l y 50% P<0.05	Further studies are needed to investigate strategies to prevent imbalance in the innate medium response to prevent or diminish inflammation and periodontal disease activity.

			ASSESSED: TREM-1 DAP-12			

Article	Author Journal	Study Design	Materials And Groups	Stastisical Analysis	Result	Limitation
Porphyromonas gingivalis regualtes TREM-1 in Human polymorpho nuclear neutrophils via its gingipains	Nagihan Bosatnci,Thomas Thumhear Plosone Journal 2013	In Vitro study	P.gingivalis wild type W50 strain and gingipain knock- out mutant K1A and E8 strain were used. All 3 starains were grown anaerobically on Columbia Blood agar plates for 3-4days at 37°in brain heart infusion broth containing 0.5%hemin and 0.2%menadione 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	One way Analysis (ANOVA) Bonfer Post hoc test Bonferron	Engagement of TREM-1 means of anti TREM-1 antibodies, enhanced the capacity of P.gingivalis to stimulate IL-8 production. Conversely anatagonism of TREM-1 using a synthetic peptide resulted in redutcion 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 starins, for better outcome.

Article	Author Journal	Study Design	Materials And Groups	Stastisical 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.Belibasak, R.Lopez, N.Bostanci JDR clinical and Translational research 2019	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	Graph pad prism software SEM Bonferron	Engagement of TREM-1 means of anti TREM-1 antibodies, enhanced the capacity of P.gingivalis to stimulate IL-8 production. Conversely anatagonism of TREM-1 using a synthetic peptide resulted in redutcion 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 starins, for better outcome.

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

expressed on myeloid cells 1 in periodontal disease	M.Willi, G.N.Belibasakis N.Bostanci 2014		One tissue sample from each subject was obtained and submerged immediately in a sterile tube RNA latter solution and Graph Pad software version 6.02 stored at -80 degree centigrade until further laboratory analysis. Total RNA and DNA were extracted from samples. The resulting DNA samples were stored at -20 degree centigrade. Methods: qPCR Human monocyte cell Biofilm super mutants ELISA	statistics program version 21 Mann Whitney U test Spearman"s range correlation Unpaired t test Bonferron	was increased in both chronic and aggressive periodontitis compared to health and correlated with the levels of red complex species in tissue. No significant differences were detected between 2 forms of periodontitis Biofilm challenged MM6 cells exhibited higher TREM-1 expression and secretion compared to controls,with partial involvement of the red complex.	TREM-1 ligand and demonstrate mechanisms behind the selective involvement of TREM-1 in cytokine regulation.

Article	Author Journal	Study Design	Materials And Groups	Statistical Analysis	Result	Limitation
Increased expression of triggering receptors expressed on myeloid cells 1 & 2 in inflamed human gingiva.	Journal of periodontal research S.S.Chen, K. Wang, J.Zahoor, W.C.Wu, Y.F.Wu, L.Zahoor.	Cross section study	Healthy Individual-31 (19males;12 females) (PD<3mm) Chronic periodontitis=53 (26 males;27 females)	Unpaired two - tailed student's T test Non parametric Mann whitney U test Spearman's rank correlation coefficient.	TREM-1, TREM-2 were also found expressed in gingival epithelial cells. TREM-1 was detected	TREM-1,TREM-2 roles in the immune response during periodontitis, but the mechanisms that contribute to their expression

	2016		(PD>6mm) (CAL>4mm) Gingival tissue samples were collected. METHOD: *Quantitative Immunohisto chemical Analysis. *Quantitative real time polymerase chain reaction. VARIABLE ASSESSED: TREM-1, TREM-2	Bonferron	in almost all gingival epithelium from both healthy and inflamed biopsie . 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.

Article	Author Journal	Study Design	Materials And Groups	Statistical Analysis	Result	Limitation
The modulation of the TREM-1/PGLYRP1 /MMP-8 axis in peri-implant disease	Clinical Oral Investigation Mayla K.S.Teixeira, Ronald Lira-Junior, Eduardo Jose Veras Lourenco, Daniel Morales Telles, Elisab eth A.Bostrom, Carlos Marcelo Figueredo, Nagihan Bostanci. 2019	Cross sectional study	Participants - 77 Healthy - 29 Gingivitis- 18 Periodontitis- 16 Mucositis - 20 GINGIVITIS GROUP: Bleeding on probing more than 20% PD<3mm CAL<1mm PERIODONTI TI S GROUPS: Bleeding on probing more than 30% PD>5mm CAL>3mm MATERIALS AND METHODS: Study includes 77 patients (29	SPSS version 24 Shapiro Wilk test Mann Whitney test Chi square test Spearman correlation coefficient Bonferron	The periodontiti s group presented higher probing depth(PD) mean and higher clinical attachment loss,compa red with the other groups.The peri-implan titi s group presented higher probing depth mean in implants compared to the mucositis group.Patie nts with PD>6mm	It's cross-section a 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.Prospe ctive studies with larger cohorts would clarify the relationship between the levels of TREM-1/PGL YRP1/MMP-8 axis in peri-implant disease It is also important to point out that

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			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.

Article	Author Journal	Study Design	Materials And Groups	Statistical Analysis	Result	Limitation
Doxycycline inhibits TREM-1 induction by porphyromonas gingivalis	Nagihan Bostanci, Georgios N. Belibasakis Federation of European microbiological societies 2012	Invitro study	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. METHOD: Cell culture Bacterial Viability Assay RNA extraction ELISA CDNA synthesis	ANOVA Bonferroni post hoc test. Bonferron	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 administration. SDD indeed inhibited P.gingivalis induced IL-8 secretion in a dose dependent manner.	It was recently demonstrated that P. gingivalis regulates the TREM-1/DAP12 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

			qPCR			needed to investigate.

Article	Author Journal	Study Design	Materials And Groups	Statistical Analysis	Result	Limitation
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	Cross sectional study	Healthy patients n=51 Periodontal disease n=17 Gingivitis n=19 Patients with chronic periodontitis n=15 GCF sampling was done with periopaper collection strips. Collected paper strips were directly placed into micro-centrifuge tubes and stored at 80c subgingival plaque - paper points- frozen at (-70c) METHOD qPCR Electronic Impedance device Fluorometric assay ELISA	Graph pad software Kruskal-Wallis one -way ANOVA and Dunn's test. Bonferron	GCF Volume,total protein concentrations, and sTERM-1 levels in GCF were similar among the groups($p>0.05$). Significantly higher T.forsythia levels were observed in subgingival plaque samples harvested from patients with gingivitis and CP, thain in those from healthy patients participants ($p<0.05$). However, the subgingival levels of other four periodontal pathogens and total bacteria ($p<0.05$).	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.

Article	Author Journal	Study Design	Materials And Groups	Statistical Analysis	Result	Limitation
Comparison of sTREM-1 and associated periodontal and bacterial factors before/ after periodontal therapy and impact of psychosocial factors l	M. Dubar, J.P. Frippiat, T.Remen, Gibot, Bisson Journal of clinical periodontology	Case control study	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	Mann whitney test Mac namara test Wilcoxon test Pearson's coefficient correlation Multivariable stepwise logistic regression SAS version 9.4 Bonferron	After SRP cervicular sTREM-1 levels decreased $p<0.001$ and were linked to a PPD decrease but remained higher in pathological than in healthy sites $p<0.001$ Higher sTREM-1 levels were associated with P.gingivalis, T.denticola, C.rectus in pathological sites after SRP $p<0.05$	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 etiopathogenes is of this disease.

Article	Author Journal	Study Design	Materials And Groups	Statistical Analysis	Result	Limitation
A Point-Of-Care Test of Active Matrix Metalloproteinase -8 (Ammp-8) Predicts Triggering Receptor Expressed on Myeloid Cells-1 (TREM-1) Levels In Saliva	Ismo T. Raisanen , Anna Maria Heikkinen , Elmira Pakbazneja D Esmaeili , Taina Tervahartiala, Riitta Pajukanta , Anjelika Silbereisen , Nagihan Bostanci And Timo Sorsa	Case control study	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	Spearman rank correlation Shapiro-Wilk test Mann-Whitney U test aMMP-8 Poc test Bonferroni correlation Bonferron	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 ($P<0.05$). In	Sample size is small Results are not definitive More research with other populations and larger sample sizes are needed to confirm our results.

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	Journal of periodontal research 2019				contrast, adolescent s with a positive aMMP-8 PoC test result (i.e. elevated aMMP-8 levels) together with elevated TREM-1 levels had significantly higher number of periodontal pockets with ≥4mm (P<0.001).	

TABLE 3: Levels Of Evidence Of The Included Articles

S.No	Author And Year	Study Design	Level Of Evidence
1.	Nagihan Bostancl.et.al 2011	In vitro study	5
2.	Mrudula varanasi.et.al 2016	In vitro study	5
3.	Nagihan Bostancl.et.al 2013	In vitro study	5
4.	A.Silberesian.et.al 2019	In vitro study	5
5.	M.Willi.et.al 2014	Invitro study	5
6.	Chen SS.et.al 2016	Cross sectional study	3b
7.	Mayls K.S.Teixeira.et.al 2019	Cross sectional study	3b
8.	Nagihan Bostancl.et.al 2012	In vitro study	5
9.	Vell Ozgen Ozturk.et.al 2016	Cross sectional study	3b
10.	Marle Dubar.et.al 2017	Case control study	3a
11.	Ismo T. Raisanen	Cross sectional study	3b

DISCUSSION

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-inflammation 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-gingipain 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-2were 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

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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.

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