Efficacy Of Low Dose Doxycycline In The Treatment Of Periodontal Disease - A Systematic Review

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Abstract: Background:Periodontal instrumentation is accessible to a certain limit, as subgingival calculus is difficult to remove completely in cases of deep pockets and furcation defects. Host modulating agents aim to inhibit arachidonic acid pathways, modulate MMPs, bone remodeling, and regulate immune and inflammatory responses. This systematic review aimsto find the effects of Low Dose Doxycycline (LDD) as local drug delivery systems and sub-antimicrobial dose doxycycline for the treatment of periodontal disease.Material And Methods: Electronic database searched were: Pubmed, Medline, Scopous and Ebsco was performed using MeSH terms: low dose doxycycline, subantimicrobial dose doxycycline, chemically modified doxycycline, doxycycline, doxycycline hyclate, atridox and periostat. Articles published between years 2008-2019 were reviewed. Result: A Systematic review methodology was followed and database searching was done which yields 422 records. Records from year 2008 – 2019 were taken into consideration. After inclusion and exclusion accordingly, A total of 10 studies were systematically reviewed. Non surgical or surgical periodontal therapy is more effective in reducing periodontal disease when low dose doxycycline is used as an adjunct either locally or systematically delivered. Conclusion: Subantimicrobial Dose Doxycycline (SDD) is commonly accepted as a host response modifier and it Subantimicrobial Dose Doxycycline (SDD) which down regulates the activity of MMPs. Also, doxycycline provides long-term post-treatment effects. Based in the inference drawn from this systematic review, non surgical or surgical periodontal therapy is more effective in reducing periodontal disease when low dose doxycycline is used as an adjunct, delivered either locally or systematically. [Slim L Natl J Integr Res Med, 2021; 12(4):66-72]

Key Words: Low Dose Doxycycline, Subantimicrobial Dose Doxycycline, Doxycycline, Doxycycline Hyclate, Atridox And Periostat

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Introduction: The tooth and its supporting structures are coated with plaque which acts as a host to a plethora of microorganisms[1]. Periodontal disease is of two types, namely acute periodontitis and chronic periodontitis. Interaction between symbiotic microbes and pathogenic microbes and the host they colonize are the main reason for periodontal tissue breakdown. The primary clinical feature includes gingival enlargement, pocket formation, loss of attachment and alveolar bone loss. The goal of periodontal therapy is to preserve, maintain and improve the health of tooth and implant supporting structures, and to reduce any future risk for the disease.

Scaling and root planning is considered the basis of periodontal therapy as it includes removal of supragingival and subgingival plaque and calculus, but to an extent[2]. Periodontal instrumentation is accessible to a certain limit, as subgingival calculus is difficult to remove completely in cases of deep pockets and furcation defects. Considering these drawbacks, host modulation therapy comes into the picture. Host modulating agents aim to inhibit arachidonic acid pathways, modulate MMPs, bone remodeling, and regulate immune and inflammatory responses[3].

Tetracycline is seen to be used widely in periodontal therapy which modulates host response to periopathogenic bacteria. It has been suggested to be used as an adjunctive therapy to scaling and root planning. Low dose doxycycline (LDD) as local drug delivery systems and sub-antimicrobial dose doxycycline administered systematically are two widely used of doxycycline for the treatment of periodontal disease, without additional systemic side-effects[4].

Material & Methods: Literature Search: This systematic review is based on PRISMA (preferred reporting items for systematic review and meta-

analysis). Literature was searched systematically and studies were identified based on the PICO (Glossary of Evidence Terms 2007): Electronic database searched were: Pubmed, Medline, Scopous and Ebsco was performed using MeSH terms: low dose doxycycline, subantimicrobial dose doxycycline, chemically modified doxycycline, doxycycline, doxycycline hyclate, atridox and periostat.

Articles published between years 2008-2019 were reviewed. The selected titles were reviewed by two authors- Lukram Slim and Sachit Anand Arora and were included based on following inclusion and exclusion criteria.

Study Selection:Focused Questions: Effects of sub antimicrobial dose doxycycline on periodontal disease pathogens. Effect of local drug delivery of doxycycline in treatment of chronic and aggressive periodontal patients.

Efficacy of low dose doxycycline in periodontal treatment. Effect of long germ use of doxycycline.

Inclusion Criteria: Systematic Review. Meta-Analysis. Cohort Study. Randomized Control Study. Human studies. Longitudinal studies. Case series.

Exclusion Criteria: Publications in any language. other than English. Animal Studies. In Vitro studies. Patients with known systemic disease. Patient on medication from last 6 months.

Results:

Study Identification: A Systematic review methodology was followed and database searching was done which yields 446 records. Additional sources yielded 24 more records. 48 duplicate records were removed, leaving 422 records to be screened further. Records from year 2008 -19 were taken into consideration[3-23].

209 records were found. 213 records were further reviewed and 88 records were excluded on the basis of availability of full texts. 125 articles were reviewed, 28 articles were excluded on the basis of language other than English.

From total of 97 records, 14 animal studies, 20 in vitro studies and 30 studies which used methodology not appropriate for this review and 23 case reports were excluded. A total of 10 studies are systematically reviewed.

Figure 1: A Prisma Chart Showing The Inclusion Of Studies In The Review Process

Outline Of Systematic Methodology

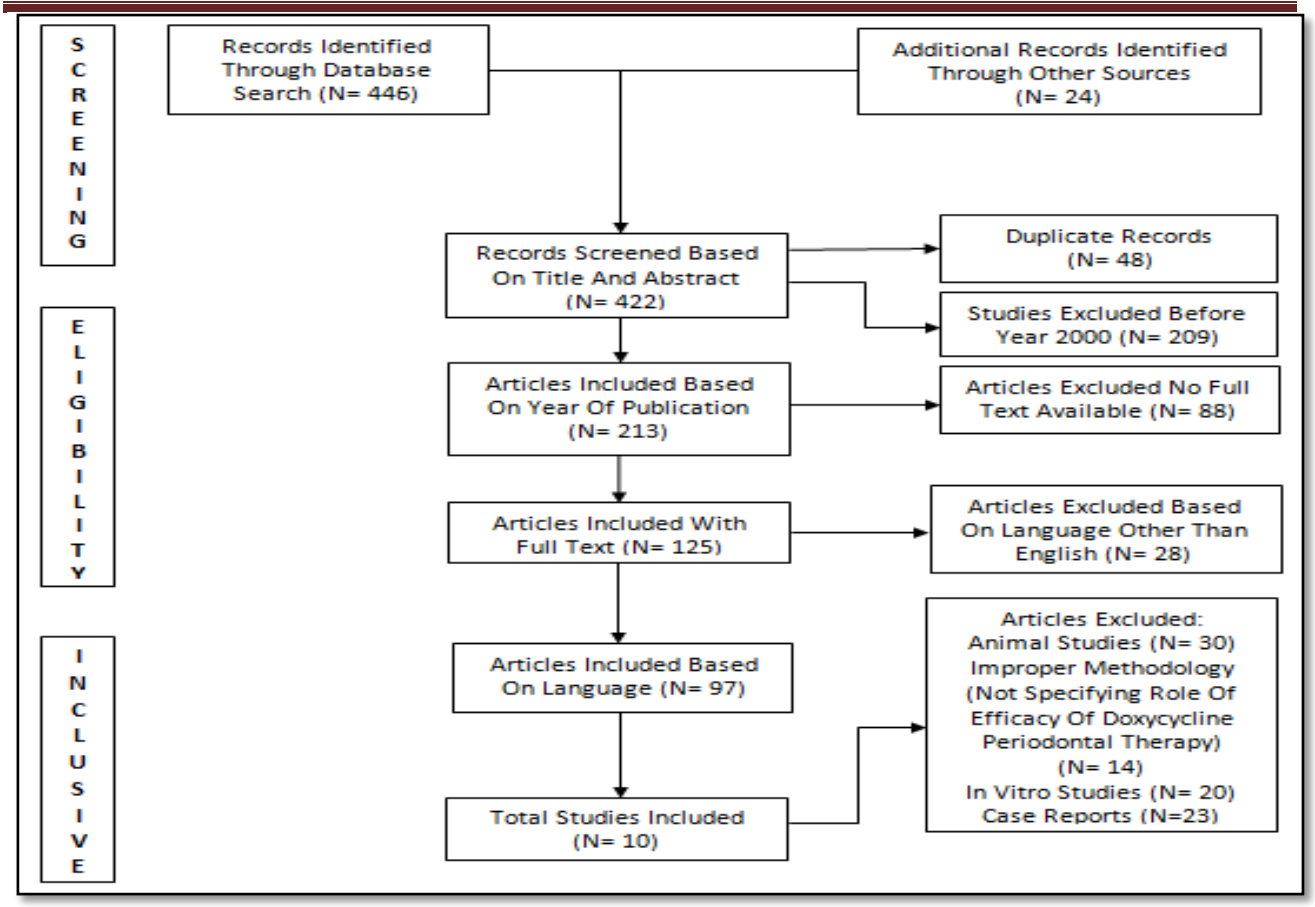

Table 1: Overview Of The Details, Study Designs, Sample Size, Age, Interventions, Parameters Significance Intervals (P Value) And Inferences

Researchers & Year	Study Design	Sample size	Age (year)	Test Groups/ Intervention	Para meter	P value	Inference
Emingil et.al 2019[24]	randomized ,double-blind, placebo-controlled, parallel-arm study	Sample Size = 30	31-61	Group A-SDD(20mg b.i.d for 3 months)+SRP Group B-PLACEBO (b.i.d. for 3 months)+SRP	PPD CAL GCF	p< 0.025	SSD+SRP showed a statistically significant improvement for all clinical parameters in the first 3 months which was maintained throughout the 12 month i.e, no statistically significant changes in clinical parameters were seen from 3-12 months
Ahamed et.al 2016[25]	Parallel design, Aclinical and microbiological study	Subject 14 Sample= 30	25-55	Control group=SRP Test group= SRP+ ATRIDOX	PPD GAL	p < 0.05	SRP+ 10% Doxycycline hyclate shows significant improvement in PPD and GAL
Pârvu AE et al 2012[27]	double-blind, placebo-controlled, randomize, 3-month clinical study with 2 treatment arms: SRP + SDD or SRP	Sample= 174	30-60	Group A= SRP+ Placebo Group B SRP+SDD	PPD CAL	p< 0.01	At the end of the 3 month trial, they were able to achieve a statistically significant result in all the clinical parameters checked.

	+placebo						
Mukhatar Ahmed Javali, K. L. Vandana 2012[26]	A randomized cross-over split mouth design,clinical study	Subject 4(2AP,2CP)130 sites	As per AAP 1999	Control groupA= SRP ,GroupB=SRP +Doxycycline GroupC= doxycycline	CAL DT	p< 0.001	doxycycline hyclate 10% gel (Atridox) is as effective as SRP in reducing the CAL and Delta Temperature
Emingil, Gu¨rkan, Atilla, Kantarci 2011[30]	randomize, doublemasked, placebo-controlled experiment	Subject = 46	34-61	Group A SRP+ SDD Group B SRP + Placebo	PPD CAL GCF	p< 0.05	In this 12 month study, a statistically significant difference was seen in PPD of the SDD group throughout the study, whereas, no improvement was seen in CAL and GCF as compared to the placebo group and from the baseline. CAL was seen to improve in both the groups in the first 3 months and was maintained throughout.
Rao et.at 2011[29]	Parallel design, single-blinded, Randomized control trial	Subject 14 (4F 10M) 20 sites	20-50	Control Group SRP+DOXYCYCLINE at baseline only Test group SRP+DOXYCYCLINE At baseline, 1 month and 3 months	PPD, RAL	p < 0.05	SRP+DOXYCYCLINE shows significant improvement in PPD and RAL
Tu¨ter, Serdar, Kurtisx, et al. 2010[28]	Randomized placebo controlled clinical trial	Sample = 58 CP=47 Healthy =17	36-51	Group A= control (healthy group)Group B=SRP+ placebo, Group C= SRP+SDD	PPD CAL GCF MMP-8 MMP-13	p < 0.001	Adjunctive SDD therapy can improve the clinical parameters, such as PPD and CAL and these clinical improvements are reflected by the controlled level of MMPs in CP patients after the therapy.
Emingil, Atilla, Sorsa, Tervahartiala 2008[32]	Randomized, double-masked, placebo-controlled, parallel-arm study	Subject= 30	37-61	Group A (SRP+ SDD) Group B (SRP+Placebo	PPD CAL GCF EMMPRIN	p< 0.025	A statistically significant result was obtained in the SRP+SDD group compared to the placebo group at 3 months and it was maintained in the later months
Bogren et. At 200[31]	Randomised Controlled Clinical Trial	Subject = 128 Sample= 30	≥20 years	Test group= 60(SPT+Local Ab)Control group = 64 (SPT)	PPD RAL	p< 0.001	Statistically significant beneficial effects on PPD and RAL were observed with the adjunctive use of locally delivered controlled-release doxycycline in periodontitis patients.
Ranjan Gupta, Nymphean Pandit, Shweta	single center, randomized, controlled trial, split	Subject= 30 90 sites	25-75 years	Control groupA-(SRP) GroupB-(SRP+ DH) GroupC-(SRP	PPD CAL	p< 0.001	Either DT or CHX, used as an adjunct have shown marked improvement than SRP alone

Aggarwal,Ashish Verma 2008[33]	mouth study.			+CHX)			

Discussion: Scaling and root planing has been considered as the gold standard for the treatment periodontal diseases but, it does not lead to major clinical improvements in cases of advanced disease and deep periodontal pockets[5].

This is probably because scaling and root planing alone does not cause a sufficiently deep change in the subgingival microbial composition to achieve and maintain a profile compatible with periodontal health longitudinally. Mechanical removal of bacterial plaque and calculus, combined with proper oral hygiene measures are known to prevent further periodontal attachment loss in most individuals by reducing total sub gingival bacteria. But, some individuals continue to experience attachment loss due to the presence of periodontal pathogens like *Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum, Treponema denticola*, etc. which invades the periodontal tissues and resides in the depth of the sulcus also in the area of furcation, where the periodontal instruments are hard to reach, or due to poor host defense mechanisms[4]. The use of SDD as an adjunctive therapy to SRP provides an additional benefits in the management of chronic periodontitis compared to periodontal non-surgical treatment alone. Also, it provided long-term post-treatment effects.

However, long-term administration of doxycycline might develop antibiotic resistance.

But, in contrary to this, studies have proven that SDD (20 mg twice daily) administered for just 2 weeks inhibited collagenase activity by 60–80% in the gingival tissues of patients with chronic periodontitis (Golub *et al*. 1990)[6]. Collagenase activity was also significantly reduced in GCF collected from these patients. This dosing regimen could prevent periodontitis progression without the emergence of doxycycline-resistant microorganisms or other typical antibiotic side-effects (Golub *et al.* 1994)[7].

Pharmacokinetic studies in human volunteers have demonstrated that 20 mg doxycycline twice daily resulted in peak serum concentrations of 0.7–0.8 mg/ml and steady-state concentrations of approximately 0.4 mg/ml (Caton 1999)[8]. This level is below the minimum inhibitory concentration (MIC) determined for doxycycline in vitro for the great majority of the bacteria isolated from subgingival plaque (Walker et al. 1985, Walker 1996)[9,10], and is well below the blood levels of 3–4 mg/ml produced by antibiotic doses of 100–200 mg (Walker *et al.* 2000). From this perspective, therefore, at a (sub antimicrobial) dose of 20 mg twice daily, doxycycline does not appear likely to exert any significant selection pressure resulting in the development of resistant strains, or have any influence on periodontal bacteria.

Doxycycline related suppression and inhibition of MMPs mainly target on three types of tissues: Epithelieum- Inhibition of production of epithelial derived MMPs by inhibiting cellular expression and synthesis.[9], Connective tissue: Directly inhibit the MMPs by cationic chelation. Inhibits the oxidative action of latent MMPs. Down regulates the expression of key inflammatory cytokines such as IL-1, IL-6, TNF-α and PGE2.

Scavenges and inhibits the production of reactive oxygen species produced by PMNs Stimulates fibroblasts and collagen production. And Alveolar bone: - Reduces the osteoclastic activity and bone resorption, Blocks osteoclast MMPs, Stimulates osteoblast activity and bone formation.

The aim of the present systematic review is to check the efficacy of low dose doxycycline in treatment of periodontal diseases. By the term low dose doxycycline, we understand that low dose of doxycycline could be in the form of sub-antimicrobial oral dose or what is known as local drug delivery.

Clinical parameters such as PPD, CAL, DT, RAL, GCF (MMP-8,-13, EMMPRIN) can be used to check the effectiveness of the drug during a certain period of the time of the study. This systematic review evaluated published studies showing the efficacy of low dose doxycycline, delivered systematically or locally, for the treatment of periodontal diseases.

In a series of studies conducted by *Emingil et al.*

(2019,2011,2008)[24,30,32,] comparing the sub-antimicrobial dose doxycycline with placebo drugs, a statistically significant result was achieved in the SDD group, with marked improvement in PPD, CAL and RAL. The results were consistent throughout the course of the studies. Tuter *et. al*. in their randomised placebo controlled clinical trial showed statistically significant decrease in PPD in the group which received SDD as an adjunct to SRP.

Paruv *et al.* concluded in their study that SRP with SDD as an adjunctive gives a statistically significant result in the first three months.

Ahamed S. *et al.* concluded that that 10% doxycycline gel used as an adjunct therapy to scaling and root planning shows significant improvement in the parameters along the study period of 180 days. Microbial analysis has also shown significant improvement at 90 days.

K.L.Vandana *et al.* in their study 10% doxycycline alone nor SRP alone didn't provide any statistically significant result whereas, doxycycline when used as an adjunct provided a statistically significant result. for the same.

Rao *et al*[29]*.* in 2011 conducted a parallel designed, randomized control trial showed that there were no statistically significant results between PPD and RAL as, doxycycline is effective for treatment of periodontal diseases whether given at baseline only or at baseline and 3 months both. In another study by *Bogren et al.* comparing surgical periodontal therapy with and without local drug delivery of doxycycline. Results stated that patients who received doxycycline with SPT showed statistically significant PPD and RAL compared to SPT alone. Gupta R. *et a*l. showed a statistically significant improvement in the PPD and CAL of the two groups where an adjunct were used, compared to the group where only SRP was given along the time period of the study.

Based in the inference drawn from this systematic review, non surgical or surgical periodontal therapy is more effective in reducing periodontal disease when low dose doxycycline is used as an adjunct either locally or systematically delivered.

Conclusion: Periodontitis is a group of diseases characterized by destruction of the periodontal attachment apparatus supporting the teeth. It has been well established that periodontal disease is the result of bacterial infection. The elimination of these microbial pathogens in the subgingival space is the primary objective of periodontal therapy. The treatment of periodontal diseases consists mainly of mechanical debridement of the affected root surface (which is considered a gold standard) along with reducing the total bacterial load and changing the environmental conditions of these microbial niches, and here comes the role of antibiotics.

Various antibiotics such as minocycline, tetracycline, metronidazole, and hexidine and anti‑ inflammatory agents, such as flurbiprofen and triclosan, have been used for the treatment of periodontitis in the past years.

Tetracycline family (tetracycline, minocycline and doxycycline) and an antiseptic consisting of chlorhexidine are more commonly used. Of these, subantimicrobial dose doxycycline (SDD) is commonly accepted as a host response modifier and it subantimicrobial dose doxycycline (SDD) which down regulates the activity of MMPs. Also, doxycycline provides long-term post-treatment effects.

Subantimicrobial doses, doxycycline is an inhibitor of matrix metalloproteases, and has been used in various experimental systems. With the understanding of periodontal disease and the treatment methods, various local delivery systems have been designed without the systemic side effects of antibiotics.

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Conflict of interest: None
Funding: None
Cite this Article as: Slim L, Arora S, Gilani F. Efficacy Of Low Dose Doxycycline In The Treatment Of Periodontal Disease - A Systematic Review. Natl J Integr Res Med 2021; Vol.12(4): 66-72