Use of Subantimicrobial Dose Doxycycline as Adjunct Therapy in Periodontitis Patients: Rapid Review

Yanti Rusyanti[1]*, Budhi Cahya Prasetyo[1], Regita Nurjinggan Audiani[2]

1. Dept. of Periodontics Dentistry, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia.
2. Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia.

Abstract

Periodontitis is an inflammatory disease of periodontal tissue due to pathogenic microorganisms interacting with host responds. Treatment scaling and root planing have been established as the standard in treating periodontitis, but there are limitations. The combination of additional therapy using Subantimicrobial Dose Doxycycline (SDD) is needed to overcome the excessive host response so that it can produce better therapeutic results. This study aims to determine the development of science regarding using SDD as an adjunct therapy in periodontitis patients.

Rapid review method with literature screening and selection using the PRISMA protocol. The search strategy was carried out on the PubMed, Science Direct, and ProQuest databases using keywords and Boolean operators according to predetermined inclusion and exclusion criteria.

Five articles reviewed showed various changes in clinical parameters and inflammatory mediators. Changes in parameters that are considered significant and insignificant but still offer a better direction.

The whole article shows that SDD positively affects the periodontal tissue, as seen by the decrease in Probing Depth (PD), Clinical Attachment Level (CAL), Bleeding on Probing (BOP), Gingival Index (GI), Plaque Index (PI), Matrix Metalloproteinase (MMP) and Gingival Ctevicular Fluid (GCF) which play a significant role in periodontitis.

Review (J Int Dent Med Res 2022; 15(4): 1798-1805)

Keywords: Doxycycline, host modulation, periodontitis.

Received date: 04 July 2022 **Accept date:** 31 August 2022

Introduction

Periodontitis is a chronic inflammatory disease of the periodontal tissue induced by bacterial in the oral cavity and affect the masticatory function and loss of teeth.[1,2,3] Based on Riskesdas 2018 data, the prevalence of periodontitis in people aged 15 years is 67.8%. This percentage shows that seven out of ten Indonesians have periodontitis.[4] Periodontitis is characterized by swelling and bleeding of the gingiva which is called gingivitis. If ignored, gingivitis can lead to more serious stage of gingival disease, called periodontitis. The main signs of periodontitis are bleeding gums, edema, the appearance of periodontal pockets, loss of attachment and may cause bad breath (halitosis).[5] Periodontal tissue damage that occurs not only comes from the inflammatory response of plaque bacteria but there is also the involvement of host immune response factors.[6] The host immune systems are important defense mechanisms that protect the periodontal tissue, but if the immune systems response continues, serious damage occurs to both soft and hard periodontal tissues.[6,7]

Scaling and root planing is a common dental procedures to treat chronic periodontal disease. This treatment is performed to remove local irritating factors such as bacterial plaque and calculus that play a role in the development of gingival and periodontal disease.[8,9] To achieve reduction or elimination of pathogens, a subgingival application of antiseptics and antibiotics has often been considered as an adjunctive

Corresponding author:
Yanti Rusyanti
Department of Periodontics Dentistry, Faculty of Dentistry, Universitas Padjadjaran, Bandung, Indonesia.
E-mail: yantirusyanti@yahoo.co.id

therapy, in conjunction with scaling and root planning. However, long-term use allows an increase in resistance to antibiotics, causing treatment to become ineffective.[10,11]

Along with the development of knowledge and understanding, there is a new therapeutic agents for the treatment of periodontal diseases, called Host Modulation Therapy (HMT). Host modulation therapy (HMT) is considered to provide better treatment outcomes.[12]

A variety of drugs have been evaluated as host modulation agents, but only Subantimicrobial Dose Doxycycline (SDD) that have been approved by the Food and Drug Administration (FDA) USA, UK Medicines and Healthcare Products Regulatory Agency as an adjunctive therapy after scaling and root planing in the treatment of periodontitis. SDD is a 20 mg dose of doxycycline taken twice a day for 3 - 9 months. The long-term used of SDD did not cause development of drug-resistant bacterial strains and considered quite safe, and also relatively cheap.[10,13,14,15,16] Based on the study of Caton et al.(2003), Novak et al. (2002) and Presaw et al. (2003), SDD can be used both in chronic periodontitis, aggressive periodontitis, periodontitis patient with smoking habits or diabetes mellitus.[17,18,19] Another study conducted by Golphar et al. also showed that the SDD group had more significant changes in clinical parameters.

On this day, there have been no review articles that have reviewed the latest research on this subject, so this prompted the authors to conduct a rapid review study on the use of SDD as adjunctive therapy in periodontitis patients based on the results of recent studies. It is hoped that this research generating new knowledge and insight, may become a reference for future research, and be useful for practitioners in considering the use of SDD as an adjunctive therapy for periodontitis patients.

Materials and methods

The type of research used is a rapid review with research characteristics using PICO. The population in this study were periodontitis patients, Intervention was scaling root planing with a subantimicrobial dose of doxycycline, Comparison was additional therapy using placebo, and Outcome was clinical parameters of periodontal tissue such as CAL or PD or BOP as the primary assessment and mediator of inflammation. The inclusion criteria in this study were articles that were relevant to the research topic, based on full text, in English or Indonesian, published within the last 10 years, from 2011 – 2021 and with the type of randomized controlled trial. Meanwhile, the exclusion criteria in this study were articles that were not accessible, the research subjects were animals and did not explain the clinical parameters of periodontal in the research results.

The selecting and screening procedure was carried out using the PRISMA protocol. Article searches were carried out in the PubMed, Science Direct and ProQuest databases using the Boolean Operators "AND" and "OR" adjusted for each database, and keywords of subantimicrobial dose doxycycline OR SDD OR doxycycline AND periodontitis. Five articles were then reviewed as shown in the chart in figure 1.

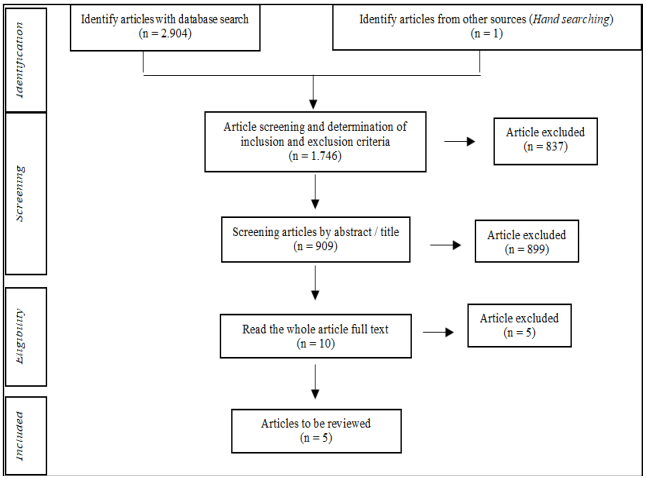

Figure 1. Screening Flow and Study Selection Based on PRISMA.

Results

After the PRISMA analysis, five articles were analyzed. Data taken from the articles listed in the table in research titles, year of publication, participants, interventions, parameters, research results and conclusions. The results of data extraction can be seen as in table 1.

Discussion

Based on table 1, the effect of Subantimicrobial Dose Doxycycline (SDD) as adjunctive therapy in periodontitis patients can be seen through changes in clinical parameters such as Probing Depth (PD), Clinical Attachment Level (CAL) and Bleeding on Probing (BOP), and also other parameters such as the Gingival Index (GI), Plaque Index (PI), Approximal Plaque Index (API) and MMP–9 and MMP-13 as inflammatory mediators. In a study conducted by Emingil et al. (2019), SDD is proven to give positive results after 3 months. The test group which was given a 20 mg dose of doxycycline (SDD) twice a day at 1 hour before meals, as well as the control group which was only given a placebo, showed a significant decrease in Probing Depth (PD), meanwhile the decrease difference of Probing Depth in both group was insignificant.[10] The results of this study are in line with the study of Gilowski et al. (2012), Pârvu et al. (2013) and Attia et al. (2020).[20,21,22] This decrease is associated with the anti-inflammatory and anticollagenase properties in SDD, so that it can improve the healing process in periodontal tissues.[23]

Not only assessing the decrease in PD, but also assessing other clinical parameters such as Clinical Attachment Level (CAL), Gingival Index (GI), Plaque Index (PI) and Bleeding on Probing (BOP). The decreases in CAL, PI and GI were significant in the study of Emingil et al. (2011 & 2019).[10,24] The results of the CAL assessment are in line with the research of Gilowski et al. (2012) and Pârvu et al. (2013).[20,21] Emingil et al. (2019) also stated that SDD as an adjunctive therapy has more clinical benefits compared to scaling and root planing therapy alone, the effect not only lasting for 3 months but also until the end of the study period, which is 12 months.[10] The clinical improvement was associated with the long-term host modulating effect, which the role in inhibiting MMP regulation, and SDD has anti-inflammatory properties.[1,23,25] Gilowski et al. (2012) also evaluated the Approximal Plaque Index (API) in patients with chronic periodontitis with diabetes mellitus as the percentage of plaque present in the approximal space and evaluated Bleeding on Probing (BOP) by observing the location of bleeding after probing. The BOP assessment was performed at four sites in each tooth and was expressed as a percentage. The evaluation stated that there were significant results in the test group and that there were insignificant differences when a comparison was made between the two groups.[21] The BOP assessment was in line with the results obtained by Pârvu et al. (2013).[20]

The mechanism of tissue damage in periodontal disease is related to the presence of Matrix Metalloproteinase (MMP) enzymes. MMP will result in the destruction of the extracellular matrix which then causes bone resorption.[26] SDD as a host modulating agent down regulates expression of main inflammatory cytokines, osteoclasts and regulation of the MMP matrix, resulting in collagen destruction and reduce loss of attachment of connective tissue and alveolar bone. [13,14,17,27] This statement is proven by research conducted by Attia et al. (2020) that there was a significant decrease in MMP-9 and MMP-13 levels in both groups, but the decrease in MMP levels was more significant in the test group (the group that was given SDD as adjunctive therapy) than the control group, either at one month after therapy or three months after therapy.[22] The improvement of clinical parameters in all

articles is associated with the mechanism of action of SDD as a host modulating agent that can reduce tissue damage and regenerate periodontium by regulating the reduction of the destructive aspects of the host response and regulating the enhancement of the immune response, so it can increase the stability of the periodontal tissue.[28,29]

Research conducted by Gilowski et al. (2012) and Emingil et al. (2019) also assessed the levels of Gingival Crevicular Fluid (GCF) in the test group and control group.[10,21] In the study of Gilowski et al. (2012), the decrease in GCF only occurred in the test group, while in the study of Emingil et al. (2019) found a significant decrease in both groups.[10,21] As we know, an increase in GCF volume is associated with the severity of inflammation.[21] The results of this study show good results, submicrobial doxycycline has been shown to inhibit GCF in periodontitis patients.[14] The concentration of hemoglobin (HbA1c) in the blood in periodontitis patients with diabetes mellitus was assessed by Gilowski et al. (2012).[21] The results of the analysis showed that there was no significant difference, in fact there was no change in the concentration of HbA1c before and after therapy in the two groups. These results are not in line with previous studies conducted by Kardeşler et al. (2010) and Engebretson et al. (2011) who assessed a significant decrease in HbA1c levels after 3 months of therapy. Further research is needed to assess the differences in HbA1c concentrations after periodontal therapy.[30,31]

Many studies have shown that short-term use of SDD can inhibit inflammation, however long-term used of SDD did not cause development of drug-resistant bacterial and has no adverse effect on normal periodontal microflora.[10] This research is supported by Ciancio and Ashley, they proved that long-term use of SDD (1 year) did not cause any side effects and did not produce microbial resistance. Laboratory diagnosis also showed no effect on liver or kidney function.[32] So far, the use of SDD is recommended for adjunctive therapy in overcoming the limitations of scaling and root planing and the problem of antibiotic drug resistance in periodontitis patients who are considered less in providing effective therapeutic results and satisfying.

Conclusions

All articles studied showed that the use of subantimicrobial dose of doxycycline produced a good effect on periodontal tissue. This is supported by the results of the evaluation of clinical parameters and other parameters that are considered significant. The evaluation of clinical parameters were assessed in the values of PD, CAL, BOP, GI and PI, API, MMP and GCF. However, the whole article only provides a dose of 20 mg SDD in 3 months, there is no recent study that provides SDD in the long term, so more updated research is needed to evaluate the long-term effects of SDD.

Acknowledgements

This article get no funding support from any resource grant.

Declaration of Interest

The authors report no conflict of interest.

No	Title, Author and Year of Publication	Participant	Intervention	Parameters	Result	Conclusion
1.	**Subantimicrobial-Dose Doxycycline and Cytokine – Chemokine Levels in Gingival Crevicular Fluid (Emingil *et al.* 2011)**	***Randomized, double-blind, placebo-controlled study, parallel-arm study.*** n = 46, aged 34 – 61 years old with the following criteria: • Suffering from chronic periodontitis • No history of systemic disease. • No hypersensitivity to the tetracycline group. • Not doing periodontal treatment and taking drugs that affect the periodontal tissue in the last 4 months. • Not pregnant or breastfeeding,	Test group (n=23): • GCF sampling using filter paper. • SRP • Given 20 mg SDD for 3 months. (in the morning and in the evening, 1 hour before eati) • OHI Control group (n=23): • GCF sampling using filter paper. • SRP • Given a placebo capsule for 3 months. (in the morning and in the evening, 1 hour before eat) • OHI	• PD • CAL • GI • PI • GCF	**PD (mm)** • Test group 6.9 ± 1.4 to 2.9 ± 1 • Control group 6.3 ± 1.5 to 3.4 ± 1.1 **CAL(mm)** • Test group 7.2 ± 1.6 to 5.7 ± 3 • Control group 7.5 ± 1.5 to 6.3 ± 1.8 **GI** • Test group 2.2 ± 0.4 to 0.4 ± 0.7 • Control group 2.1 ± 0.3 to 1.2 ± 0.9 **PI** • Test group 3.6 ± 1.4 to 1.2 ± 0.8 • Control group 4.1 ± 1.1 to 2.3 ± 1.7 **GCF (µl)** • Test group 0.5 ± 0.2 to 0.2 ± 0.1 • Control group 0.5 ± 0.2 to 0.2 ± 0.1	The impact of using SDD can produce long-term host modulation effects and good changes in clinical parameters even if only for 3 months. The increase can also be maintained for up to 12 months.
2.	**Efficacy of short-term adjunctive subantimicrobial dose doxycycline in diabetic patients – randomized study. (Gilowski *et al.* 2012)**	***Randomized, double-blind, placebo-controlled study.*** N = 34, age 36-68 years old with the following criteria: • Have at least 14 teeth • 6 months before the study was clinically diagnosed with type 2 diabetes mellitus. • Individuals with severe or moderate chronic periodontitis. • 4 mm PD at 4 nonadjacent tooth sites. • Did not receive prophylaxis and periodontal treatment in the last 6 months. • No hypersensitivity to tetracycline. • Do not smoke • No history of systemic disease • Not pregnant or breastfeeding. • Receive optimal diabetes treatment.	Test group: • Prescreening check of GCF sample collection 1 week post prescreening • SRP • Given additional 20 mg dose of SDD for 3 months (2 times a day in the morning and evening, 1 hour before meals with 12 hour intervals) • Clinical measurements, GCF samples and blood samples were collected after 3 months of treatment. Control group: • Prescreening check • GCF sample collection 1 week post prescreening • SRP • Given placebo for 3 months. • Clinical measurements, GCF samples and blood samples were collected after 3 months of treatment.	• PD • CAL • API • BOP • GCF • HbA1c	**PD** • Test group 4.03 ± 0.82 to 2.42 ± 0.55 • Control group 4.15 ± 0.80 to 2.89 ± 0.62 **CAL(mm)** • Test group 4.71 ± 1.14 to 2.42 ± 0.55 • Control group 5.19 ± 1.20 to 4.84 ± 1.10 **API (%)** • Test group 90.0 to 50.0 • Control group 75.0 to 63.6 **BOP (%)** • Test group 37.5 to 14.4 • Control group 30.8 to 20.5 **GCF (µl)** • Test group 0.97 to 0.79 • Control group 0.85 to 0.9 **HbA1c (%)** • Test group 6.7 to 6.7 • Control group 6.2 to 6.3	This study assessed changes in clinical parameters and HbA1c levels after 3 months of SDD therapy in diabetic patients. The results showed no significant changes except in PD, the average value of HbA1c also did not show any change.
3.	**Efficacy of subantimicrobial-dose doxycycline against nitrosative stress in chronic periodontitis. (Pârvu *et al.* 2011)**	***Double-blind, placebo-controlled, randomized, 3 month clinical study.*** n = 174 with the following criteria: • Age 30 – 60 years old • Have at least 16 teeth with 3 teeth in the same sextant.	Test group (n=87): • SRP • Given 20 mg doses of SDD (twice a day, 1 hour before meals at 12 hour intervals) for 3 months. • Visits were made 8 times	• PD • BOP • CAL	**PD(mm)** • Test group 5.90 ± 0.16 to 3.25 ± 0.42 • Control group 6.18 ± 0.22 to 3.42 ± 0.37 **BOP (%)** • Test group	Host modulation therapy using SDD in patients with moderate to advanced chronic periodontitis can provide improvements in the clinical index of periodontal tissue. This correlates with reduced nitrosative stress, so

		• 5 mm PD with BOP in at least 2 locations. • Clinical attachment level (CAL) 5 mm. • Radiographic evidence of loss of alveolar bone height. • Do not take drugs that can affect the periodontal status. • Not breastfeeding or pregnant. • Do not have an allergy to tetracycline. • Do not smoke. • Do not suffer from infectious diseases and are immunocompromised.	Control group (n=87): • SRP. • Given placebo capsules (twice a day) • Visits were conducted 8 times.		65.4 ± 1.02 to 23.70 ± 1.12 • Control group 66.00 ± 2.50 to 44.60 ± 3.10 **CAL(mm)** • Test group 5.80 ± 1.50 to 3.90 ± 1.20 • Control group 5.69 ± 0.50 to 4.1±0.81	it can counteract both local and systemic inflammatory responses.
4.	**Adjunctive Effects of a Sub-Antimicrobial Dose of Doxycycline on Clinical Parameters and Potential Biomarkers of Periodontal Tissue Catabolism. (Emingil *et al.* 2019)**	***Randomized, double-blind, placebp-controlled study.*** n = 30 with the following criteria: • Age range 31 – 61 years old. • Have at least 14 teeth. • Individuals with stage III periodontitis. • Periodontitis was diagnosed from a 3 mm CAL with pockets > 3mm detectable in at least 2 teeth. • No history of systemic disease or hypersensitivity to any type of tetracycline. • Not taking antibiotics, other drugs or periodontal treatment in the last 4 months. • Not pregnant or breastfeeding • Not a heavy addict of alcohol or tobacco. • For patients who smoke, do not smoke more than four cigarettes per day.	Test group (n=15): • Periodontal status measurement using a William probe at 6 sites per tooth. • GCF sample collection. • Performed 4-6 sessions of non-surgical periodontal therapy by the same doctor as the control group. • The tooth surface and roots are instrumented under local anesthetic until free of deposits. • OHI instructions. • Given additional SDD (20 mg per capsule) for 3 months and taken 2 times a day, 1 hour before meals. Control group (n=15): • Periodontal status measurement using a William probe at 6 sites per tooth. • GCF sample collection • Performed 4-6 sessions of non-surgical periodontal therapy by the same doctor as the test group. • The tooth surface and roots are instrumented under local anesthetic until free of deposits. • The control group received an additional placebo capsule for 3 months. • OHI Instructions	• PD • CAL • GI • PI • GCF	**PD (mm)** • Test group 7.05 ± 0.72 to 2.90 ± 1.04 • Control group 6.68 ± 1.15 to 3.55±1.40 **CAL (mm)** • Test group 7.58 ± 1.49 to 4.90±2.16 • Control group 7.90 ± 1.69 to 6.35±2.09 **GI** • Test group 2.11 ± 0.49 to 0.26 ± 0.39 • Control group 1.78 ± 0.59 to 0.43±0.61 **PI :** • Test group 3.68 ± 0.87 to 1.32±0.84 • Control group 4.05 ± 1.18 to 2.18±1.31 **GCF (µl)** • Test group 1.12 ± 0.35 to 0.50±0.24 • Control group 0.98 ± 0.40 to 0.53 ± 0.28	Additional use of a subantimicrobial dose of doxycycline showed significant improvement in clinical parameters. Although the duration of use was only 3 months, the improvement in clinical parameters persisted until the 12th month.
5.	**Effect of Subantimicrobial Dose Doxycycline Treatment on Gingival Crevicular Fluid Levels of MMP-9 and MMP-13 in Periodontitis Stage 2, Grade B in Subjects with Type 2 Diabetes Mellitus. (Attia *et al.* 2020)**	n = 30, Type 2 diabetes patients aged 36-48 years old with the following criteria: • Patients diagnosed with stage 2 periodontitis, grade B according to Papapanou et al. • Individuals with a CAL of 3 – 4 mm and bone loss limited to the coronal 1/3 of the root (radiographically). • No tooth loss due to periodontitis. • PD 5 mm. • Diagnosed with Type 2 Diabetes Mellitus with HbA1c levels < 7.0% • No other systemic disease.	Test group (n=15): 1. SRP 2. Given 20 mg dose of SDD (twice a day for 3 months). 3. GCF sample collection using periopaper points. Control group (n=15) 1. SRP 2. GCF sample collection using periopaper points.	• GI • PI • PD • MMP-9 • MMP-13	**GI** • Test group 0.97 ± 0.41 (1 month) 1.27 ± 0.74 (3 months) • Control group 0.73 ± 0.45 (1 month) 0.67 ± 0.55 (3 months) **PI** • Test group 1.50 ± 0.51 (1 month) 1.73 ± 0.52 (3 months) • Control group 1.40 ± 0.56 (1 month) 1.57 ± 0.57 (3 months) **PD** • Test group 1.23 ± 0.43 (1 month)	SRP combined with consumption of Subantimicrobial Dose Doxycycline (SDD) resulted in significant changes in clinical and biochemical parameters in stage 2 periodontitis, grade B accompanied by type 2 diabetes mellitus compared to SRP therapy alone.

	• Not pregnant or breastfeeding. • No previous periodontal treatment or antimicrobial therapy in the past 6 months.	1.40 ± 0.50 (3 months) • Control group 1.13 ± 0.51 (1 month) 1.37 ± 0.61 (3 months) **MMP-9** • Test group 770.11± 308.88 (1 month) 999.62 ±396.83 (3 months) • Control group 347.24 ± 183 (1 month) 572.58 ±303.28 (3 months) **MMP-13** • Test group • 257±177.38 (1 month) • 1076.83± 390.94 (3 months) • Control group • 181.67 ± 69.73 (1 month) • 968.33 ± 609.19 (3 months) *number is the total reduction of parameters within 1 month and 3 months

Table 1. Data Extraction.

References

1. D'Aiuto F, Gkranias N, Bhowruth D, Khan T, Orlandi M, Suvan J, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. lancet Diabetes Endocrinol. 2018;6(12):954–65.
2. Ermawati T. Periodontitis dan Diabetes Melitus. STOMATOGNATIC-Jurnal Kedokt Gigi. 2015;9(3):152–4.
3. Suratri MAL. Pengaruh Hipertensi Terhadap Kejadian Penyakit Jaringan Periodontal (Periodontitis) pada Masyarakat Indonesia (Data Riskesdas 2018). Bul Penelit Kesehat. 2020;48(4):227–34.
4. Kemenkes RI. Hasil Riset Kesehatan Dasar Tahun 2018. Kementrian Kesehat RI. 2018;53(9):1689–99.
5. Gurav AN. Management of diabolical diabetes mellitus and periodontitis nexus: Are we doing enough? World J Diabetes. 2016;7(4):50.
6. Shalu B. Textbook of Periodontics. Jaypee Brothers,Medical Publishers Pvt. Ltd.; 2017:394.
7. Deshmukh J, Jawali MA, Kulkarni VK. Host modulation therapy–a promising new concept in treating periodontal diseases. Int J Dent Clin. 2011;3:48–53.
8. Zulfa L, Mustaqimah DN. Terapi periodontal non-bedah non-surgical periodontal therapy. J Dentomaxillofacial Sci. 2011;10(1):36–41.
9. Gross AJ, Paskett KT, Cheever VJ, Lipsky MS. Periodontitis: a global disease and the primary care provider's role. Postgrad Med J. 2017;93(1103):560–5.
10. Emingil G, Gürkan A, Tervahartiala T, Hernandez M, Özgül S, Sorsa T, et al. Adjunctive effects of a sub-antimicrobial dose of doxycycline on clinical parameters and potential biomarkers of periodontal tissue catabolism. Dent J. 2019;7(1):9.
11. Rams TE, Degener JE, Van Winkelhoff AJ. Antibiotic resistance in human chronic periodontitis microbiota. J Periodontol. 2014;85(1):160–9.
12. Wulandari P. Terapi Modulasi Host : Sebagai Salah Satu Terapi Periodontal. Terapi Modulasi Host: Sebagai Salah Satu Terapi Periodontal. 2015. p. 348–54.
13. Kaur M, Krishan K. Subantimicrobial dose doxycycline in treatment of periodontitis. Periodontol. 2017;3:1472–83.
14. Carranza M, Newman G, Takei H, Perry R, Klokkevold A, Carranza F. Clinical Periodontology. 2015:526
15. Payne JB, Golub LM, Stoner JA, Lee H, Reinhardt RA, Sorsa T, et al. The effect of subantimicrobial-dose–doxycycline periodontal therapy on serum biomarkers of systemic inflammation: a randomized, double-masked, placebo-controlled clinical trial. J Am Dent Assoc. 2011;142(3):262–73.
16. Shinwari MS, Tanwir F, Hyder PR, Bin Saeed MH. Host modulation therapeutics in periodontics: role as an adjunctive periodontal therapy. J Coll Physicians Surg Pak. 2014;24(9):676–84.
17. Caton JG, Ciancio SG, Blieden TM, Bradshaw M, Crout RJ, Hefti AF, et al. Treatment with subantimicrobial dose doxycycline improves the efficacy of scaling and root planing in patients with adult periodontitis. J Periodontol. 2000 Apr;71(4):521–32.
18. Novak MJ, Johns LP, Miller RC, Bradshaw MH. Adjunctive benefits of subantimicrobial dose doxycycline in the management of severe, generalized, chronic periodontitis. J Periodontol. 2002 Jul;73(7):762–9.
19. Preshaw PM, Hefti AF, Bradshaw MH. Adjunctive subantimicrobial dose doxycycline in smokers and non-smokers with chronic periodontitis. J Clin Periodontol. 2005 Jun;32(6):610–6.
20. Pârvu AE, Alb SF, Crăciun A, Taulescu MA. Efficacy of subantimicrobial-dose doxycycline against nitrosative stress in chronic periodontitis. Acta Pharmacol Sin. 2013 Feb;34(2):247–54.
21. Gilowski L, Kondzielnik P, Wiench R, Płocica I, Strojek K, Krzemiński TF. Efficacy of short-term adjunctive subantimicrobial dose doxycycline in diabetic patients--randomized study. Oral Dis. 2012 Nov;18(8):763–70.
22. Attia MS, Alblowi JA. Effect of Subantimicrobial Dose Doxycycline Treatment on Gingival Crevicular Fluid Levels of MMP-9 and MMP-13 in Periodontitis Stage 2, Grade B in Subjects with Type 2 Diabetes Mellitus. J Immunol Res. 2020 Nov:2807259.
23. Garrido-Mesa N, Zarzuelo A, Gálvez J. What is behind the non-antibiotic properties of minocycline? Pharmacol Res [Internet]. 2013;67(1):18–30. Available from: https://www.sciencedirect.com/science/article/pii/S1043661812001934
24. Emingil G, Gürkan A, Atilla G, Kantarci A. Subantimicrobial-dose doxycycline and cytokine-chemokine levels in gingival crevicular fluid. J Periodontol. 2011 Mar;82(3):452–61.
25. Walker C, Thomas J, Nangó S, Lennon J, Wetzel J, Powala C. Long-term treatment with subantimicrobial dose doxycycline exerts no antibacterial effect on the subgingival microflora associated with adult periodontitis. J Periodontol. 2000 Sep;71(9):1465–71.
26. Checchi V, Maravic T, Bellini P, Generali L, Consolo U, Breschi L, et al. The Role of Matrix Metalloproteinases in Periodontal Disease. Int J Environ Res Public Health [Internet]. 2020;17(14):4923. Available from:

https://www.proquest.com/scholarly-journals/role-matrix-metalloproteinases-periodontal/docview/2423110664/se-2
27. Fitri H, Fajrin FN, Kasuma N, Suharti N. Efek pemberian zink pasca scaling root planning terhadap kadar MMP-8 saliva pada pasien gingivitis. B-Dent J Kedokt Gigi Univ Baiturrahmah. 2019;6(2):132–41.
28. Narketpally ND. Host modulation therapy-restriction of periodontal destruction. IJDA. 2011;3(3):621.
29. Bartold PM, Van Dyke TE. Host modulation: controlling the inflammation to control the infection. Periodontol 2000. 2017;75(1):317–29.
30. Kardeşler L, Buduneli N, Çetinkalp Ş, Kinane DF. Adipokines and inflammatory mediators after initial periodontal treatment in patients with type 2 diabetes and chronic periodontitis. J Periodontol. 2010;81(1):24–33.
31. Engebretson SP, Hey-Hadavi J. Sub-antimicrobial doxycycline for periodontitis reduces hemoglobin A1c in subjects with type 2 diabetes: A pilot study. Pharmacol Res [Internet]. 2011;64(6):624–9. Available from: https://www.sciencedirect.com/science/article/pii/S1043661811002167
32. Golub LM, Lee H. Periodontal therapeutics: Current host-modulation agents and future directions. Periodontol 2000. 2020;82(1):186–204.