Literature Review

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Clinical response of doxycycline administration to periodontal tissues of periodontitis patients with type 2 diabetes mellitus: Rapid Review

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ABSTRACT Diabetes mellitus is a group of physiological dysfunctions due to insulin resistance and inadequate insulin secretion characterized by hyperglycemia. Diabetic patients have an increased risk and severity of periodontitis. Therefore, additional periodontal treatment is required. Doxycycline is a broad-spectrum antibiotic and has the anti collagenase ability to inhibit tissue damage. This study aims to determine the clinical response of periodontal tissue in patients with periodontitis with type 2 diabetes mellitus to doxycycline. This rapid review was conducted online in May-July 2021 on randomized controlled trial articles about systemic doxycycline as an adjunctive periodontal treatment in periodontitis patients with type 2 diabetes mellitus. The search was carried out from three electronic databases, Pubmed NCBI, Cochrane Library, and Google Scholar concerning PRISMA analysis guidelines, using PICO strategy and the study quality assessed by SORT. Five articles were selected with good evidence quality (level 1). Probing pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), plaque index (PI), gingival index (GI), and gingival recession were evaluated. The result showed a more significant reduction in clinical parameters in periodontitis patients with type 2 diabetes mellitus who received additional systemic doxycycline treatment, except gingival recession. Systemic doxycycline as an adjunctive periodontal treatment in periodontitis patients with type 2 diabetes mellitus gave a positive clinical response, with better results than no other doxycycline treatment group.

KEYWORDS: Doxycycline, periodontitis, diabetes mellitus

INTRODUCTION

Diabetes mellitus is a group of physiological dysfunctions that occurs due to insulin resistance, inadequate insulin secretion, or both with the characteristic of hyperglycemia.[1] Prolonged hyperglycemia can cause molecular and cellular effects on the body that causes an increased inflammatory response, susceptibility to infection, impaired healing, and predisposes to various complications.[2,3,4,5] Diabetes mellitus is one of the most rapidly growing public health problems globally.[6,7] According to the International Diabetes Federation, in 2019, 463 million adults had diabetes mellitus. They would continue to increase until it was estimated that in 2045, 700 million people would suffer, which 90%-95% of sufferers were people with type 2 diabetes mellitus.[7,8]

The analysis results of the National Health and Nutrition Examination Survey in Korea in 2010-2015 showed that people with diabetes mellitus had a 3-4 times higher risk of periodontitis than those who did not have diabetes.[9] The study also stated that adults with type 2 diabetes mellitus had a higher frequency of gingival inflammation than non-diabetic patients, and the highest level of inflammation was seen in patients with poor glycemic control.[9] For years, the relationship between diabetes and periodontitis has been suspected.[10] Diabetes is believed to be a risk factor and a modifying factor for periodontitis.[3] Periodontitis is also the 6th complication of diabetes besides retinopathy, nephropathy, neuropathy, cardiovascular disease, and peripheral vascular disease.[11]

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Periodontitis is a chronic inflammation of the supporting tissues of the teeth that causes progressive loss of the periodontal attachment and alveolar bone.[12,13,14] The primary etiologic factor of periodontal disease is bacteria which are substantially present in the human oral cavity.[15,16] However, most of the damage results from inappropriate host response, such as the hyperinflammatory response associated with diabetes.[17] Periodontitis is a pathological condition of the oral cavity that many people widely suffer.[15] According to the 2016 Global Burden of Disease Study, periodontal disease ranked as the 11th most common condition with a prevalence ranging from 20%-50% worldwide.[18,19] In Indonesia, most periodontitis is still relatively high, namely 74,1%.[20] The number of sufferers of periodontitis made WHO in its report entitled "Equity Social Determinants and Public Health Programmes" stated that periodontal disease was one of the essential oral diseases included as a public health problem that requires action.[21]

Periodontitis is generally treated with nonsurgical mechanical debridement. However, surgical treatment may also be indicated in specific patients.[22] Nonsurgical treatment is an action that aims to control periodontal infection by removing biofilm bacteria, calculus, and toxins from the tooth surface using various methods such as hand instruments, ultrasonic and sonic scalers, as well as ablative laser therapy.[23,24] Considering the incidence and increasing severity of periodontitis in diabetic patients, nonsurgical periodontal treatment alone is insufficient.[17,25] During the last few years, antibiotics usage as an adjunctive periodontal treatment has been carried out.[26] Various studies showed that antibiotic usage as an adjunctive periodontal treatment provides better clinical and microbial outcomes.[26,27] Various antibiotics such as amoxicillin, metronidazole, azithromycin, and doxycycline have been used to treat periodontitis.[28] Doxycycline is a broad-spectrum antibiotic, bacteriostatic in nature, and effective against the proliferation of various types of bacteria. In addition, doxycycline also has anti collagenase abilities that can inhibit tissue damage and help bone regeneration.[29] It is the new therapeutic approaches basis in controlling periodontal disease, not only in healthy people but also in people with specific conditions such as diabetes mellitus.[30]

Based on the conditions described, the author felt it was necessary to study doxycycline's effect on the periodontal tissues' clinical state in periodontitis patients with type 2 diabetes mellitus. Effective treatment is needed given the rapid development of type 2 diabetes mellitus cases and plays an essential role in increasing the risk and severity of the periodontal disease. Therefore, this review was carried out to find out how the clinical response of doxycycline administration to the periodontal tissues in periodontitis patients with type 2 diabetes mellitus

RESULTS

Study search results

Study search was conducted through 3 electronic databases using predefined keywords. The study search results in the databases identified 75 articles; 23 articles came from Pubmed NCBI, 45 reports were obtained through the Cochrane Library, and Google Scholar found 7 articles. The initial screening was done by selecting articles published in 2010-2020 so that 47 articles were obtained. The second screening was done by checking for duplication. In this examination, 10 articles were excluded so that 37 articles were obtained. The third screening was done by selecting the title and abstract so that 19 articles were accepted, followed by the fourth screening by reading the entire contents of the article to see the suitability of the content with the research topic so that 14 articles were excluded and five reports were obtained that would be studied as research samples. The study search flowchart is presented in **Figure 1**.

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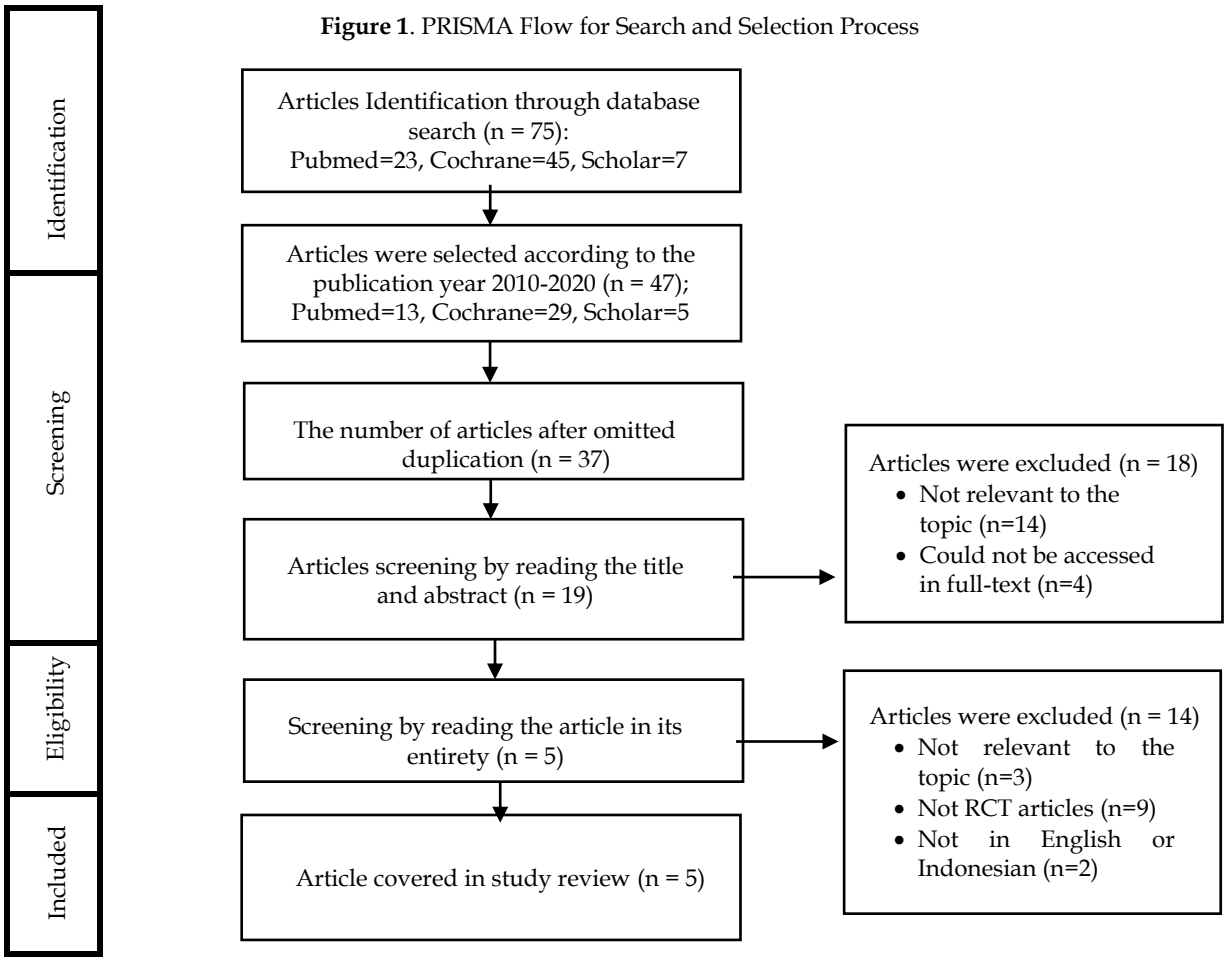
Table 1. Reasons for Study Exclusion

Exclusion Criteria	Number of Screened Articles
Articles not relevant to the topic	17
Articles not randomized controlled trial studies	9
Articles that could not be accessed in full-text	4
Articles not in English or Indonesian	2
Total	32

Figure 1. PRISMA Flow for Search and Selection Process



Study Characteristics

The total number of selected and reviewed articles was five articles with a randomized controlled trial study design.[32,33,34,35,36] Based on the assessment results of the evidence quality using the Strength of Recommendation Taxonomy (SORT) guidelines, five reviewed articles had good evidence quality (level 1). The characteristics of the articles covered are presented in **Table 2**.

Table 2. Study Characteristics

Author (Year)	Title	Study Design	SORT	Number of Samples	Sample Origin	Intervention	Parameters	Measurement Method
Al-Nowaiser AM et al. (2014)[32]	Evaluation of adjunctive systemic doxycycline with nonsurgical periodontal therapy within type 2 diabetic patient	RCT	Level 1	68	Saudi Arabia	**Test** : Scaling and root planing with systemic doxycycline 100 mg/day for 14 days with an initial dose of 200 mg on the first day (administered 45 days after SRP) **Control** : Scaling and root planning	1. Periodontal pocket depth (PPD) 2. Clinical attachment level (CAL) 3. Gingival index (GI) 4. Plaque index (PI) 5. Bleeding on probing (BOP)	Manual Florida Probe at 6 sites
Gilowski et al (2012)[33]	Efficacy of short-term adjunctive subantimicrobial dose doxycycline in diabetic patients--randomized study	RCT	Level 1	34	Poland	**Test** : Scaling and root planing with doxycycline hydrochloride 20 mg for 3 months (consumed once in the morning and once in the evening 1 hour before meals, with an interval of 12 hours) **Control** : Scaling and root planing with placebo	1. Periodontal pocket depth (PPD) 2. Clinical attachment level (CAL) 3. Plaque index (PI) 4. Bleeding on probing (BOP)	William Probe at 6 sites
Das AC et al. (2019)[34]	Adjunctive Effect of Doxycycline with Conventional Periodontal Therapy on Glycemic Level for Chronic Periodontitis with Type 2 Diabetes Mellitus Subjects	RCT	Level 1	51	India	**Test** : Scaling and root planing with systemic doxycycline (total dose of 1,600 mg equally divided into 16 doses, started with 100 mg 2 times daily, continued 1 time daily for 14 days) **Control**: Scaling and root planing	1. Periodontal pocket depth (PPD) 2. Clinical attachment level (CAL) 3. Gingival index (GI) 4. Plaque Index (PI)	N/A
Deo V et al. (2010)[35]	Evaluation of subantimicrobial dose doxycycline as an adjunct to scaling and root planing in chronic periodontitis patients with diabetes: a randomized, placebo-controlled clinical trial	RCT	Level 1	20	N/A	**Test** : Scaling and root planing with doxycycline hyclate 20 mg, twice a day for 6 months **Control** : Scaling and root planing with placebo, twice a day	1. Periodontal pocket depth (PPD) 2. Clinical attachment level (CAL) 3. Gingival recession	William Probe at 6 sites (PPD) and 4 sites (CAL)

Tsalikis L et al. (2014)[36]	Effects of doxycycline on clinical, microbiological and immunological parameters in well-controlled diabetes type-2 patients with periodontal disease: a randomized, controlled clinical trial	RCT	Level 1	66	Greece	**Test** : Scaling and root planing with doxycycline 200 mg as initial dose and 100 mg/day for 20 days **Control** : Scaling and root planing with placebo	1. Periodontal pocket depth (PPD) 2. Clinical attachment level (CAL) 3. Bleeding on probing (BOP) 4. Gingival recession	Automated Florida Probe at 6 sites

Test: The group that received doxycycline treatment; Control : The group that did not receive doxycycline treatment

A total of one study article was conducted in Saudi Arabia[32], and other study articles were shown in Poland[33], India[34], and Greece.[36] However, one article did not indicate the location of the study.[35] Three of the five articles examined the intervention of 100 mg systemic antimicrobial doxycycline usage, with a duration usage from 14 days[32,34] to 20 days.[36] Two other articles conducted a study of 20 mg systemic sub-antimicrobial doxycycline, with the minimum usage of 3 months[33] and six months.[35] Various periodontal parameters were assessed in this article, including periodontal pocket depth (PPD) assessed by five articles[32-36], clinical attachment level (CAL) assessed by five articles[32-36], bleeding on probing (BOP) assessed by three articles.[32,33,36] Three articles assessed the plaque index (PI)[32-34], two articles assessed the gingival index (GI)[32,34], and gingival recession assessed in two articles[35,36]. Various methods, such as manual[32], carried out an assessment of clinical parameters and automatic Florida probes usage[36] at six sites, two articles carried out the evaluation using William Probes at six locations. Still, one other article did not indicate the assessment method.[34]

The total participants included in this study were 222 participants, consisting of the test group, namely the group of patients who received doxycycline adjunct therapy intervention, and the control group, namely the participants who did not receive doxycycline therapy. Two articles stated that each of 17 participants was in the test group and control group.[33,34] One article stated that 35 participants were in the test group, and 33 were in the control group.[32] Another report stated that the study's test and control groups were ten people each.[35] One article stated that 31 participants were test group, and 35 participants were in the control group.[36] Two articles reported that the age range of study participants was >30 years[34,36]. One article stated that the age criteria for the participants were 21 to 80 years[32], one article reported the age range of the participants was 36 to 68 years[33], and another article stated that the average age of the participants was 37,1 years[35]. Patients with controlled diabetes were the criteria for two articles[34,36], and two articles also stated that diabetes mellitus had to be diagnosed at least one year before the study[32,36]. Meanwhile, in one article, diabetes had to be diagnosed at least six months earlier[33], and one study article did not report the criteria for diabetes mellitus in the study.[35] All articles had inclusion criteria that participants should not have any medical conditions other than diabetes mellitus.[32-36] One article stated the inclusion criteria were at least 16 remaining teeth and at least eight sites with PPD and CAL $\geq$5mm[32], the other article criteria was at least 14 teeth and four sites with PPD $\geq$4mm[33], another article stated that participants must have $\geq$20 teeth with 30% of them had PPD $\geq$4mm[34], and in one other article participants had at least six sites with PPD $\geq$5mm and CAL $\geq$3 mm[36]. Four out of a total of five articles stated periodontal treatment in six months before, antibiotics usage in three months before the study, participants with smoking habits, and mothers pregnancy or lactation were the exclusion criteria[32,33,34,36], two articles stated the exclusion criteria for hypersensitivity or allergy to tetracycline/doxycycline, two other articles mentioned the use of drugs contraindicated to doxycycline as an exclusion criterion[32,33]. The characteristics of the participants are presented in **Table 3**.

Table 3 Participant Characteristics

	Participant Characteristics	Number of Articles
Number of participants in the study (test/control)	17 / 17 participants	2
	35 / 33 participants	1
	10 / 10 participants	1
	31 / 35 participants	1
Age range of participants	≥ 30 years	2
	21-80 years	1
	36-68 years	1
	Average age of 37,1 years	1
Diabetes mellitus criteria	Controlled diabetes	2
	≥ 1 year diagnosis	2
	≥ 6 months diagnosis	1
	N/A	1
Inclusion criteria	No other serious medical conditions	5
	There were at least 16 teeth with 8 PPD sites PPD ≥ 5 mm and CAL ≥ 5 mm	1
	There were at least 14 teeth with 4 PPD sites ≥ 4 mm	1
	There were at least 20 teeth with 30% PPD ≥ 4 mm	1
	There were at least 6 sites with PPD > 5 mm and CAL > 3 mm	1
Exclusion criteria	Received periodontal treatment 6 months before	4
	Received antibiotic treatment 3 months before	4
	Smoking	4
	Pregnant and breastfeeding	4
	Hypersensitivity/allergy to tetracycline/doxycycline	2
	Using drugs contraindicated to doxycycline	2

Test : The group that received doxycycline treatment
Control : The group that did not receive doxycycline treatment
PPD : Periodontal pocket depth
CAL : Clinical attachment level

Synthesis of study data covered

The review results of five articles revealed that all participants experienced positive changes after treatment, which the reduction of various clinical parameters could be seen compared to before treatment was carried out..[32-36] A total of five articles[32-36] reported that reduced pocket depth (PPD) occurred more in the test group that received doxycycline than in the control group that did not receive doxycycline. Study article Al-Nowaiser et al. (2014)[32] reported a significant reduction in pocket depth ($p<0.01$) in both groups; in patients who received doxycycline at the time of re-evaluation in 45 days after treatment, it could be seen a reduction of 0.93 mm, whereas a reduction of only 0.88 mm in the control group. Then, the study also reported that the decline in pocket depth after more than three months of treatment was more visible in the test group.[32] The study article by Gilowski et al. (2012)[33] did not present quantitative data but stated that the reduction in the pocket depth of ≥4 mm was more significant in the test group than in the control group. Research Das et al. (2019)[34] showed that in three months after treatment, the average reduction in pocket depth in the test group was very significant ($p<0.001$), namely 1.01 mm. Meanwhile, the average reduction was only 0.76 mm in the control group. Study article Deo et al. (2010)[35] also reported that after six months, both groups showed a significant reduction in pocket depth ($p<0.05$), while the reduction in the test group was 0.52 mm greater at 3.06±0.30 mm compared to 2.54±0.10 mm in the control group. The study by Tsalikis et al. (2014)[36] reported that in 3 months after treatment, both groups experienced a significant reduction in pocket depth with more reduction seen in the control group, but after six months of treatment, a greater reduction was seen in the test group. The study also stated that the group that received doxycycline had fewer sites with pocket depth of ≥5 mm than the control group (47 sites vs. 89 sites).[36]

The study by Gilowski et al. (2012)[33] did not show quantitative data but stated that both groups experienced a significant reduction in clinical attachment level (CAL) value. A total of 2 articles stated that the reduction in clinical attachment level (CAL) value was more visible in the test group.[34,35] Meanwhile, the other two articles reported a reduction in clinical

attachment level (CAL) was more reduced in the control group.[32,36] The Study article by Al-Nowaiser et al. (2014)[32] reported that after six months of treatment, it could be seen the reduction in clinical attachment level of 0.74 mm in the test group and a reduction of 0.96 mm in the control group. However, no significant difference could be observed between the two groups.[32] Similar to the study of Tsalikis et al. (2014), [36] reported that the reduction in clinical attachment level after six months of treatment was more visible in the control group than the test group. In contrast to the research of Das et al. (2019)[34] stated that the average reduction in clinical attachment level of 0.93 mm after three months of treatment was seen in the test group, which was statistically very significant ($p<0.001$). In contrast, the average reduction was only 0.73 mm in the control group. Another article by Deo et al. (2010)[35] showed the average decrease in clinical attachment level 6 months after treatment of 2.25±0.09 mm in doxycycline recipients and only 1.58±0.25 mm in the group did not receive doxycycline. Statistically, both groups experienced a significant reduction ($p<0.05$).[35]

The three articles reviewed in this study reported changes in the percentage of bleeding on probing (BOP).[32,33,36] The three articles said that the reduction in BOP was more visible in the test group than in the control group.[32,33,36] The study by Al-Nowaiser et al. (2014) showed that the percentage reduction in the BOP in six months after treatment was more significant in the test group than in the control group. The study by Gilowski et al. (2012)[33] reported a significant decrease in BOP percentage ($p<0.01$) occurred in both groups, with a more considerable reduction seen in the test group. However, no statistically significant difference ($p>0.05$) could be observed between the test and control groups.[33] Likewise with Tsalikis et al. (2014),[36] their study showed that the reduction in BOP value was seen more in the group that received doxycycline than the group that did not receive doxycycline. However, after six months of treatment, both groups experienced an increase in the BOP.

The plaque index was assessed in 3 articles.[32,33,34] Two of the three articles reported a more significant reduction in plaque index value seen in the test group.[33,34] The study by Gilowski et al. (2012)[33] stated that all participants experienced a significant reduction of plaque index ($p<0.01$), but a more substantial reduction occurred in the test group. The study by Das et al. (2019)[34] reported that within three months, the average plaque index reduction was very significant ($p<0.001$) in the test group, namely 1.33 and only 0.95 in the control group. In contrast to the other two articles, the study by Al-Nowaiser et al. (2014) reported a more significant reduction in plaque index value seen in the control group than in the test group.

A total of two articles examined the gingival index.[32,34] One report stated that a more significant reduction in the gingival index was seen in the test group.[34] Meanwhile, another article noted that the decline was more critical in the control group.[32] Das et al. (2010)[34] reported that within three months, the reduction in the gingival index value in the test group was very significant ($p<0.001$), which was 0.94, while in the control group, the reduction in the gingival index value was reported at 0.81. The study by Al-Nowaiser et al. (2014)[32] stated the opposite, namely the gingival index reduction significantly was seen in the control group than in the test group.

In contrast to other parameters, a total of 2 articles reported an increase in the gingival recession value in the test group.[35,36] The study by Deo et al. (2010)[35] reported an increase in the gingival recession value by 0.80±0.28 mm after six months of treatment in the test group and by 0.93±0.15 mm in the control group. Both groups experienced a significant increase ($p<0.05$), but when compared between groups, there was no significant difference that could be observed ($p>0.05$).[35] Tsalikis et al. (2014)[36] in their study, reported that in 3 months after treatment, all participants experienced an increase in gingival recession. However, after six months of treatment, the control group experienced a reduction, while the test group increased.[36]

Table 4. Clinical Condition Characteristics

Author (Year)	Follow up	PPD average		CAL average		BOP average		PI average		GI average		Gingival Recession average		Descriptions
		Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	
Al-Nowaiser AM et al. (2014)[32]	Baseline	3,89±0,13	3,82±0,15	4,92±0,17	5,31±0,21	66±6,9%	63±5,8%	2,14±0,16	2,18±0,12	2,12±0,11	2,08±0,11			• All participants experienced significant changes in PPD, BOP, GI, PI (p<0,05) • The reduction in PPD and BOP was greater in the test group • The reduction in CAL, PI, and GI was greater in the control group • There was no significant difference in outcome between the two groups, except for GI
	45 days	2,96±0,13	2,94±0,24	4,53±0,28	4,47±0,27	31±8,4%	29±12,2%	1,68±0,18	1,61±0,11	1,97±0,14	1,54±0,15			
	One month	2,72±0,11	2,81±0,10	4,49±0,25	4,45±4,43	26±11,3%	26±8,7%	1,56±0,12	1,58±0,11	1,57±0,10	1,48±0,15			
	Three months	2.67±0,21	2,60±0,73	4,44±0,17	4,43±0,16	27±9,5%	24±9,3%	1,42±0,13	1,47±0,21	1,46±0,11	1,36±0,29			
	Six months	2,39±0,21	2,42±0,32	4,18±0,19	4,35±0,25	19±5,3%	23±6,6%	1,39±0,12	1,33±0,21	1,36±0,21	1,29±0,23			
Gilowski et al. (2012)[33]	Baseline					37,5%	30,8%	90,0%	75,0%					• Both groups experienced a significant reduction in clinical parameters • The reduction in BOP and PI was greater in the test group • There was no significant difference in clinical parameters between the two groups (p>0,05)
	Three months					14,4%	20,5%	50,0%	63,6%					
Das AC et al. (2019)[34]	Baseline	3,31±0,62	3,08±0,30	3,76±0,66	3,79±0,40			2,50±0,42	1,99±0,43	2,04±0,33	1,80±0,39			• The reduction in PPD, CAL, PI, GI was greater in the test group than in the control group • There was no significant difference between the
	Three months	2,30±0,45	2,32±0,28	2,83±0,52	3,06±0,42			1,17±0,22	1,04±0,28	1,10±0,21	0,99±0,28			

									test and control group (p>0,05), except in PI (p<0,01)
Deo V et al. (2010)[35]	Baseline	5,66±0,50	5,73±0,22	6,05±0,25	6,03±0,45			0,39±0,26	0,32±0,22	• Both groups experienced significant improvement (p<0,05). • The reduction in PPD and CAL was greater in the test group • The test and control group had increased gingival recession • The increase in gingival recession was greater in the control group
	Six months	2,60±0,33	3,19±0,13	3,80±0,23	4,45±0,30			1,19±0,20	1,25±0,19	
Tsalikis L et al. (2014)[36]	Baseline	3,01±0,77	3,03±0,73	3,73±0,88	3,77±1,24	0,48±0,39	0,36±0,28	0,78±0,73	0,75±0,89	• Both groups experienced significant improvement (p<0,05) • The reduction in PPD and BOP was greater in the test group • The reduction in CAL was greater in the control group • Both groups experienced increased recession after 3 months • After six months, recession in the test group increased, whereas in the control group reduced
	Three months	2,46±0,52	2,29±0,56	3,27±0,77	3,16±1,38	0,11±0,19	0,11±0,1	0,82±0,64	0,87±1	
	Six months	2,17±0,5	2,27±0,57	3,02±0,67	2,87±0,89	0,12±0,16	0,12±0,12	0,85±0,55	0,61±0,62	

Test: The group that received doxycycline treatment
PPD: Periodontal pocket depth
CAL : Clinical attachment level
BOP : Bleeding on probing

Control: The group that did not receive doxycycline treatment
PI : Plaque Index
GI : Gingival index

This study was conducted to examine the clinical response of periodontal tissue to systemic doxycycline in periodontitis patients with type 2 diabetes mellitus. The assessment of the clinical condition of the periodontal tissue was carried out by looking at various clinical parameters such as periodontal pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), plaque index (PI), gingival index (GI), and gingival recession. Based on the review results of the five articles[32-36], all participants showed a positive response after treatment seen by reducing various parameters. It was aligned with the study by Gaikwand et al. (2013)[37] and Mai et al. (2020)[38] that reported that the participants after treatment with or without doxycycline showed a reduction in clinical parameters.

Periodontal treatment is an action carried out to maintain and protect dental health.[39] Scaling and root planing (SRP) are the gold standard treatment for periodontitis patients, but in recent years various treatment strategies have been proposed to improve the outcome of SRP.[40] It is done because, in certain individuals, tissue damage can still be found, which may be related to the presence of pathogenic bacteria outside the instrument's reach or due to poor host defense mechanism.[26]

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia.[41] Prolonged hyperglycemia can lead to various complications, including oral complications such as periodontal disease.[42] Various mechanisms such as disruption of the oral environment that promotes bacterial overgrowth[43] to change in host response are associated with increased periodontal disease in diabetic patients.[44] The study conducted by Aemaimanan P et al. (2013) stated that glycemic control could affect the number of red-complex bacteria in the subgingival biofilm.[45] The results showed that red-complex bacteria, especially *Porphyromonas gingivalis*, were more commonly found in uncontrolled diabetic patients than healthy individuals.[45] Similarly, Aoyama N et al. (2018) found an increase in the number of *Porphyromonas gingivalis* in the saliva of uncontrolled diabetic patients related to the condition of clinical parameters of periodontal tissues such as CAL and BOP.[46]

Various antibiotics are used as adjunctive therapy to improve the outcome of scaling and root planning treatment.[47] The study by Ramanauskaite et al. (2020)[48] stated that the periodontal therapy outcome could be improved by using the adjunct of systemic or local antibiotics and antiseptics. Doxycycline is a broad-spectrum antibiotic that has been used for a long time as an adjunct to periodontal therapy.[47,49] Doxycycline antimicrobial works by allosteric binding to the 30s ribosomal unit and preventing aminoacyl-tRNA associations. Doxycycline can stop the elongation phase of polypeptide chains, which causes inhibition of the production of the essential proteins, thereby stopping the growth of bacteria.[50] According to the study, 100 mg systemic antimicrobial doxycycline usage showed a significant reduction in various bacteria that caused periodontitis, such as *Tannerella forsythia* (Tf), *Porphyromonas gingivalis* (Pg), and *Prevotella intermedia* (Pi).[32,51] The reduction in pathogenic bacteria was used as the basis that doxycycline could increase the efficacy of scaling and root planning to reduce clinical parameters better.[25] The previous study conducted by Singh M et al. (2017) revealed that patients who received the adjunct of 100 mg systemic doxycycline therapy experienced better periodontal condition improvement than patients who did not receive the adjunct of doxycycline therapy.[52] Similarly, in this article, the results showed that 100 mg systemic doxycycline usage could reduce the average value of pocket depth (PPD) and bleeding on probing (BOP) better than patients who did not receive doxycycline therapy.

Besides the 100 mg antimicrobial doxycycline, this study also examined the usage of 20 mg of sub-antimicrobial doxycycline. The results showed that the 20 mg doxycycline usage with the minimum use of 3-6 months resulted in a positive periodontal tissue response, as seen by the reduction in periodontal pocket depth (PPD), clinical attachment level (CAL), bleeding on probing (BOP), plaque index (PI) and gingival recession better than in patients that did not receive doxycycline therapy. These results were aligned with the study conducted by Abdu Shehab et al. (2020)[53] and Mai et al. (2020)[38], who stated that sub-dose doxycycline therapy as an adjunct to scaling and root planing (SRP) could significantly reduce periodontal clinical parameters better than in patients who did not receive the adjunct of doxycycline therapy. When compared with 100 mg doxycycline therapy, in this study, the average reduction in pocket depth and clinical attachment levels in the 20 mg doxycycline group was seen to be 2 to 3 times better.

The reduction in these parameters occurs because doxycycline in low doses can act as a

host modulation therapy through the mechanism of the matrix metalloproteinases (MMPs) reduction, which are proteolytic enzymes that mediate periodontal damage, regardless of its antimicrobial ability.[30,35,54] Bacteria play an essential role in the existence of periodontitis, but its development depends on the host's response.[55] For a long time, studies had stated that periodontal damage was caused by destructive host enzymes such as matrix metalloproteinases (MMPs) and inflammatory mediators (prostaglandins and interleukins).[55] Excessive inflammatory response to periodontitis bacteria occurred in diabetic patients[44], characterized by increased inflammatory biomarkers such as MMP-8[56], IL-6, IL-1β, and TNF-*a*[57]. Increased production of MMP in inflamed periodontal tissues caused tissue damage.[55] Doxycycline host modulation therapy modulated the host inflammatory response and the host pathological collagenolytic response.[58] Studies on doxycycline modulating the host response had been conducted. They had shown that low-dose doxycycline could decrease inflammatory biomarkers such as MMPs and ILs associated with reduced pocket depth and clinical attachment level.[59,60] The United States Food and Drug Administration (FDA) had also approved the sub-antimicrobial doxycycline as a host modulating agent in periodontal disease.[61]

All periodontal parameters in this study experienced reduction but in contrast to gingival recession, which showed an increase after treatment.[35,36] It could happen cause after the treatment was carried out. The factors that cause periodontitis were eliminated, exudate was lost, and inflammatory cells migrated, which caused the reduction and retraction of the gingival volume that the root surface would be exposed and the recession would increase.[62] The study results conducted by Ramos UD et al. (2016)[63] also reported a similar situation with an increase in gingival recession after periodontal treatment.

The study generally showed more remarkable improvement in clinical parameters in the group that received the adjunct of doxycycline. However, the significant difference could not be demonstrated statistically compared to the group that did not receive the adjunct of doxycycline therapy. It was similar to the meta-analysis conducted by Yap KCH et al. (2019)[47] also stated that systemic doxycycline used as an adjunct of SRP did not result in significant improvement in the periodontal status or HbA1c of diabetic patients with periodontitis when compared between the doxycycline group that received and did not receive doxycycline.[47] In contrast, the study by Gaikwand et al. (2013)[37] stated that a significant reduction in PPD, CAL, and PI occurred in doxycycline recipients compared to patients who did not receive doxycycline.

This study results reported that doxycycline usage as an adjunctive periodontal therapy positively impacted and put these results aside.[47] Therefore, every clinician must always consider the pros and cons in prescribing antibiotics.[47] Systemic antibiotics in periodontitis should be limited to the patient and certain periodontal conditions such as periodontitis stage III-IV, grade C, "active" form, "refractory", and "recurrent" periodontitis.[48] The wise and appropriate usage of antibiotics is expected to reduce the possibility of resistance problems in the future. According to studies, in contrast to antimicrobial doxycycline, sub-antimicrobial doses of doxycycline are not known to cause bacterial resistance and microbiota disturbances because the doses used are too low to provide antimicrobial effects.[35,53,54] It can be used to consider the use of the type of doxycycline to be used in treatment.

Variations in participant criteria such as age and duration of diabetes were reported in this review. It was known that the increased generation and duration of diabetes were the factors associated with the increase in the periodontitis prevalence and severity, which was related to the onset of chronic inflammation.[64,65] Differences in inclusion and exclusion criteria that affected the periodontal tissue condition of the study samples and other factors such as dose and duration usage of doxycycline and the type of probe used in the assessment might influence the findings of different results between studies. Due to these limitations, studies with specific samples and intervention criteria should be included to reduce the heterogeneity of the assessed objects. It is also necessary to review more randomized controlled trials with populations and longer duration. Besides, studies about the effect of doxycycline on systemic conditions must be carried out, considering that the patient also has type 2 diabetes mellitus. In addition, it is hoped that studies on other types of doxycycline can be carried out to determine which treatment is better.

CONCLUSION

Based on the literature review conducted on five articles, it could be concluded that systemic antimicrobial doxycycline and sub-antimicrobial doses as adjunctive periodontal therapy in patients with periodontitis and type 2 diabetes mellitus gave a positive clinical response.

MATERIAL AND METHODS

This review was conducted from May to July 2021 at the Faculty of Dentistry, Universitas Padjadjaran using the rapid review method. Article retrieval was done online based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) analysis guidelines. The Strength of Recommendation Taxonomy (SORT) was used to assess the quality of scientific evidence from each study based on the assessment of the study design.[31] The study began by making questions using the PICO (patient, intervention, comparison, and outcome) model described in **Table 5**. The search was conducted by combining keywords in the NCBI Pubmed electronic database search engine, Cochrane Library, and Google Scholar using the boolean operators "AND" and "OR" (**Table 6**). Articles discussing systemic doxycycline usage as an adjunctive nonsurgical periodontal treatment in periodontitis patients with type 2 diabetes mellitus with the keywords "type 2 diabetes mellitus" or "diabetic" and "periodontal therapy" or "periodontal treatment" or "scaling and root planing" and "doxycycline"; articles in English or Indonesian; articles with a randomized controlled trial study design with a publication year limitation of 2010 to 2020 were inclusion criteria. The criteria were set due to the limited time of the study and the rules of the author's language skills, but it was hoped that the quality of the survey would remain good. Exclusion criteria in this study were articles not available in full-text because data extraction on the article could not be carried out, and articles with studies not conducted in humans were also excluded.

Table 5. Research Question Formulation Strategy Using PICO Model

Acronym	Definition	Description on study
P	Patient	Periodontitis patients with type 2 diabetes mellitus
I	Intervention	Nonsurgical periodontal treatment with the adjunct of systemic doxycycline
C	Comparison	Nonsurgical periodontal treatment without the adjunct of doxycycline/placebo
O	Outcome	Clinical response of post-treatment periodontium

Table 6. Search Strategy on Database

Basis data	Search Strategy	The number of articles
PubMed NCBI https://pubmed.ncbi.nlm.nih.gov/advanced/	#1 search ((type 2 diabetes mellitus[Title/Abstract]) OR (diabetic[Title/Abstract]))	284.569
	#2 search (((periodontal therapy[Title/Abstract]) OR (periodontal treatment[Title/Abstract])) OR (scaling and root planing[Title/Abstract]))	8.555
	#3 search (doxycycline[Title/Abstract])	14.568
	Final search : #1 AND #2 AND #3	**23**
Cochrane Library **https://www.cochranelibrary.com/advanced-search/search-manager**	#1 ("type 2 diabetes mellitus"):ti,ab,kw OR (diabetic):ti,ab,kw	99042
	#2 (periodontal therapy):ti,ab,kw OR (periodontal treatment):ti,ab,kw OR (scaling and root planing):ti,ab,kw	8665
	#3 (doxycycline):ti,ab,kw	2207
	Final search : #1 AND #2 AND #3	45
Google Scholar https://scholar.google.com/#d=gs_asd	allintitle: "type 2 diabetes mellitus" OR "diabetic" AND "periodontal therapy" OR "periodontal treatment" OR "scaling and root planing" AND "doxycycline"	**7**

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