

Efficacy of Systemic Amoxicillin–Metronidazole in Periodontitis Patients with Diabetes Mellitus: A Systematic Review of Randomized Clinical Trials

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ABSTRACT

Background: Diabetes mellitus is a metabolic illness that is non-communicable, chronic, and associated with hyperglycemia. It is caused by a combination of the incapability of tissues that exhibit sensitivity to insulin in response to its release & defective secretion of insulin by β -cells of the pancreas.

Aim: To assess efficiency of a combination of amoxicillin-metronidazole in enhancing periodontal variables in type 2 diabetes cases in comparison with standard periodontal treatment.

Materials and methods: This systematic review has been performed on four studies regarding the guidelines by the Cochrane Collaboration reporting followed the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses).

Results: All four investigations demonstrated that systemic amoxicillin-metronidazole enhanced periodontal health when utilized in combination with nonsurgical periodontal treatments. Miranda et al. & El Makaky et al. illustrated significant decreases in probing depth (PD), bleeding on probing (BOP) & clinical attachment loss (CAL) at 3 months when systemic amoxicillin-metronidazole has been utilized in comparison to deferred management or scaling & root planning (SRP) alone.

Conclusion: This systematic review proposed that the combination of nonsurgical

periodontal treatments with systemic amoxicillin-metronidazole may result in improved clinical results. Disparities have been noted in the antibiotic prescriptions' durations and dosages, as well as in the management's conducted to the control groups.

KEYWORDS: Metronidazole, Periodontitis, Systemic Amoxicillin, Diabetes Mellitus.

1. Introduction

Diabetes mellitus is a metabolic illness that is non-communicable, chronic, and associated with hyperglycemia. It is caused by a combination of the incapability of tissues that exhibit sensitivity to insulin in response to its release & defective secretion of insulin by β -cells of the pancreas (1). There are numerous complications that can result from chronic hyperglycemia, such as nephropathy, retinopathy and cardiovascular diseases, as well as severe death and morbidity. Diabetes affects over 537 million adults worldwide, which is more than 10.5 percent of the population. In the next two decades, it is anticipated that this figure will increase to 786 million (2). This illness is additionally the 9th leading cause of decreased life expectancy (3).

Periodontal illness is classified as the 6th main complication of diabetes mellitus by the American Diabetes Association. Periodontitis and diabetes are comorbid conditions, with diabetes being regarded as a risk factor that alters the periodontitis grade in the present classification of periodontal illness. Furthermore, there is a bidirectional association among periodontitis and diabetes mellitus (4,5).

It is crucial to perform a systematic and critical reevaluation of strategies of management for cases who have diabetes who present with periodontitis, given the rising occurrence of T2DM and periodontitis. In cases with diabetes, the primary objective of periodontitis management is to eliminate biofilm and plaque (6). Regardless of the case's glycemic status, biofilm control is accomplished throughout professional mechanical removal of plaque through scale and root planning, in conjunction with adjuvant case-administered plaque control measures. Prior to developing a plan of management, it is essential to assess any related complications. In cases with poorly controlled diabetes mellitus, it is essential to regulate glycemic levels prior to performing any operative or invasive periodontal procedures. Until success is attained, cases must be maintained on a strict maintenance protocol (7). To attain optimal periodontal health, concurrent treatment of diabetes mellitus is necessary.

The clinical results of cases with poorly controlled diabetes might be enhanced by adjunctive administration of systemic antibiotics, even though nonsurgical periodontal therapy (NSPT) may decrease inflammatory and clinical variables (8). The combination of metronidazole & amoxicillin has been illustrated to have a synergistic effect, resulting in a lessening in the dosage of both medications needed for biological action (9).

The goal of this investigation was to assess the efficiency of a combination of amoxicillin-metronidazole in enhancing periodontal variables in type 2 diabetes cases in comparison with standard periodontal treatments.

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2. Materials and methods

This systematic review has been performed on four studies regarding the guidelines by the Cochrane Collaboration reporting followed the PRISMA statement

Search Criteria

The specific question was as follows: "Does the administration of a systemic combination of metronidazole – amoxicillin following non-operative surgical treatments in diabetic cases with periodontitis lead to superior clinical outcomes for treatment in comparison to those who had non-surgical periodontal therapy only?"

The inclusion criteria regarding PICOS were as follows:

Population (P): Cases who have diabetes and who exhibit periodontitis.

Intervention (I): systemic combination of metronidazole – amoxicillin following nonsurgical treatment of periodontitis.

Comparison (C): non- surgical periodontal treatments, either only or in conjunction with systemic antibiotics other than metronidazole –amoxicillin.

Outcome (O): pocket DP (1st result parameter) &/or decreased hemorrhage on probing & clinical attachment level (2nd result parameters).

Studies (S): randomized clinical experiments & clinical control trials with a monitoring period of at least three months.

An investigation protocol has been developed for identifying randomized controlled trials that were performed between periodontitis cases who have type 2 diabetes mellitus to compare the effectiveness of non- surgical periodontal treatments in combination with systemic amoxicillin–metronidazole to that of non- surgical periodontal treatments alone or in combination with other systemic antibiotics. The 1st result parameter was a decrease in pocket probing depth, while the 2nd results parameters were CAL and bleeding on probing.

Screening & Selection of Studies

The electronic databases of Scopus, Science Web, and MEDLINE (PubMed) have been searched to identify pertinent articles. Full-text digital copies of articles written in the English language have been taken into account. The strategy of search utilized a combination of following keywords: metronidazole, nonsurgical therapy, amoxicillin, systemic antibiotics, and periodontitis. The abstracts & titles of the search findings have been independently screened by 2 reviewers. The inclusion criteria have been assessed against the resulting investigations following the removal of duplicate articles. The full texts of all investigation that were potentially relevant have been obtained for evaluation against the specified inclusion criteria. The findings have been synthesized only after the investigations that met the criteria had been further evaluated. The list of reference of the articles that were involved has been evaluated to determine whether any investigations met the inclusion criteria.

Extraction of Data

In Microsoft Excel (Microsoft Inc., Redwood, California, the United States), customized tables have been designed for extraction of data. Relevant data from the investigations that were chosen, such as the year of publication and authorship, design of investigation, results, sample characteristics, and inferences, were independently extracted by two reviewers. Disagreements have been resolved through discussion with a 3rd reviewer. Additional variables, such as the number of participants in each chosen investigation, biomarker levels, microbiological parameters, tooth mobility, and any reported adverse impacts, have been additionally recorded and evaluated in the data extraction table.

Assessment of Risk of Bias in Selected Studies

The Cochrane Collaboration's Tool for Assessing Risk of Bias Version 2.0 (ROB 2 tool) has been utilized by 2 authors to independently estimate the risk of bias (10). The validity of data has been evaluated in relation to five domains: randomization bias, selection bias, lacking outcome data, measurement bias, and difference from the intended intervention. The outcomes have been classified as low bias, some concerns, & high bias, with disagreements being resolved through discussion with a 3rd reviewer.

3. Results

The initial search resulted in 1027 articles, 825 duplicates were removed, 202 were submitted to title and abstract screening, 37 articles met our eligible criteria were assessed for full text, finally we have only four studies involved in our systematic review. Figure 1; illustrated our PRISMA flow chart for selection process of investigation.

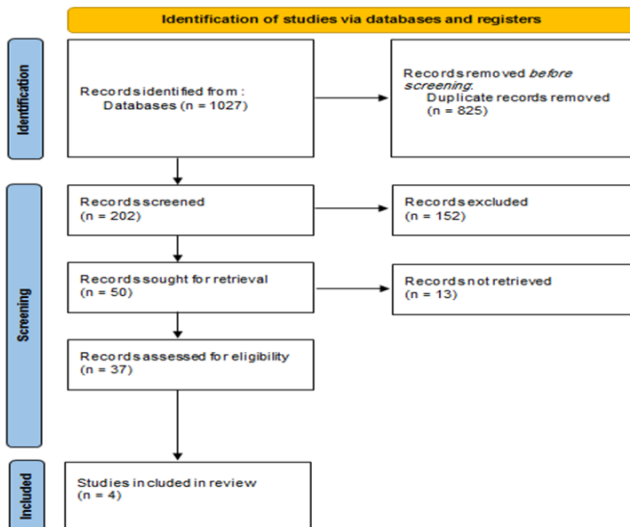


Figure 1: PRISMA flow chart for selection process of investigation.

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The characteristics of the investigation involved are presented in Table 1. The number of participants in the studies was 207 patients, geographical distribution included Egypt, Brazil and Mexico.

Table 1: general characteristics of our involved investigation.

Study No.	Study ID	Site	Study design	Sample size	intervention
1	El-Makaky (11)	Egypt	Test group: Full mouth root planing and scaling + amoxicillin (five hundred milligram TID for Two weeks) + metronidazole (four hundred milligrams TID for two weeks); Control group: No Therapy has been utilized throughout the three-month monitoring, following which therapy was the similar as that utilized in the test group (delayed therapy)	88	Amoxicillin (Five hundred milligrams TID for two weeks) + metronidazole (Four hundred milligrams TID for two weeks)
2	Miranda et al. (12)	Brazil	Test group: SRP + amoxicillin (Five hundred milligrams TID for fourteen days) + metronidazole (Four hundred milligrams TID for fourteen days); Control group: SRP + placebo	56	Amoxicillin (Five hundred milligrams TID for fourteen days) + metronidazole (Four hundred milligrams TID for fourteen days)
3	Gómez-SandovalJR et al. (13)	Mexico	amoxicillin + MET group: Standard periodontal treatment + amoxicillin (Five hundred milligrams TID for seven days) + MET (250 milligrams three times a day for seven days); Clindamycin group: Standard periodontal treatment + clindamycin (Three hundred milligrams TID for seven days) + placebo (TID for seven days)	42	Amoxicillin (Five hundred milligrams g TID for Seven days) + metronidazole (250 milligrams three times a day for days)
4	Mendonca et al., (14)	Brazil	NSD group: SRP + amoxicillin (Five hundred milligrams TID for ten days) + metronidazole (Four hundred milligrams TID for ten days); SD group: Open fla debridement + AMX (Five hundred milligrams TID for ten days) + metronidazole (four hundred milligrams TID for ten days)	21	SRP + amoxicillin (Five hundred milligrams TID for ten days) + metronidazole (Four hundred milligrams TID for ten days)

Quality of the Evidence:

Depend on ROB1, all involved experiments showed some concerns in bias assessment except Mendonca et al, that shows low risk of bias. Risk of bias graph & summary have been illustrated in figure 2 and Table 2.

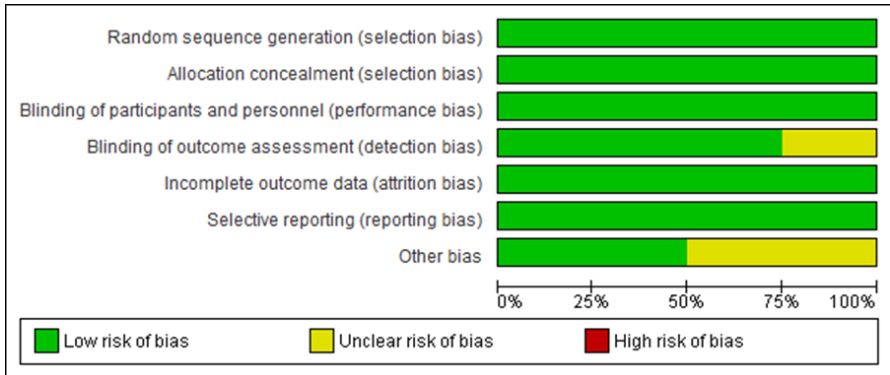


Figure 2: Risk of bias graph.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
El-Makaky 2019	+	+	+	?	+	+	+
Gómez-SandovalJR et al. 2020	+	+	+	+	+	+	?
Mendonca et al., 2012	+	+	+	+	+	+	+
Miranda et al. 2014	+	+	+	+	+	+	?

Table 2: Risk of bias summary.

Studied Outcomes:

Characteristics of Interventions:

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Of the four investigations (11, 12, 13, 14), three of them assessed effectiveness of metronidazole – amoxicillin as an adjuvant to non-operative management (11, 12), while one of them compared metronidazole – amoxicillin as an adjunct to operative treatment versus non-operative treatment.

Miranda et al. (12) & El Makaky et al. (11) utilized five hundred milligrams of amoxicillin and four hundred milligrams of metronidazole three times a day for fourteen days.

Gomez-Sandoval et al. (13) utilized five hundred milligrams of amoxicillin & 250 milligrams metronidazole TID for seven days, & Mendonca et al. (14) utilized five hundred milligrams of amoxicillin and four hundred milligrams of metronidazole

TID for ten days.

Adverse events, including headache, diarrhea, and metallic taste, were documented in two investigations (12, 14). Nevertheless, neither investigation revealed any statistically significant distinctions among the treatment groups. Two investigations didn't record any adverse impacts (11, 13).

Characteristics of Outcome Measures:

The 1st results of all four investigations included the evaluation of bleeding on probing, PD & clinical attachment level (11-14).

Some research assessed additional parameters, including plaque indexes and concentrations of HbA1c (11).

Both serum concentrations of HbA1c and sub-gingival microflora were assessed by Miranda et al. (12). In saliva, Mendonca et al. determined the number of remaining pockets & the concentration of cytokines (14).

The manual periodontal probe (North Carolina, Hu-Friedy, Chicago, Illinois, United States) has been utilized to measure PD, CAL, and BOP in the investigations that were involved. Six sites around all teeth, with the exception of third molars, have been assessed for PD and CAL. BOP has been dichotomously documented as either "yes" or "no" depending on the presence or absence of hemorrhage for all teeth, with the exception of 3rd molars.

Characteristics of Outcomes:

Systemic amoxicillin–metronidazole was demonstrated to enhance periodontal health when administered in combination with NSPT in each of the four investigations. Miranda et al. & El Makaky et al. reported a bigger decrease in bleeding on probing, probing depth, & clinical attachment level at three months when systemic amoxicillin–metronidazole has been utilized in comparison to delayed therapy (11) or SRP alone (12).

The microbial species cultured from sub-gingival biofilm have been additionally evaluated by Miranda et al., who found a decrease in the numbers of *T. forsythia*, *Eubacterium nodatum*, *Prevotella intermedia*, *P. gingivalis*, and *T. denticola* in the test group in comparison with the control group (12).

Gomez-Sandoval et al. conducted a comparison between systemic metronidazole – amoxicillin and systemic clindamycin–placebo & found statistically insignificant distinctions among the two groups in terms of a decrease in pocket PD and other clinical variables, including POB and plaque index (13).

Mendonca et al., conducted a comparison between non-operative and operative therapies in combination with systemic amoxicillin–metronidazole. Although both treatment groups exhibited a decline in probing depth & the number of residual pockets, the surgical group exhibited a more significant decrease (14).

4. Discussion

In cases with poorly controlled diabetes, NSPT, which includes scaling and root planning, in conjunction with cases motivation and education, has been demonstrated to be efficient in decreasing inflammatory and clinical variables. Nevertheless, there is a scarcity of proof regarding the additional administration of antibiotics, antimicrobials, or antiseptics in nonsurgical periodontal therapy (15). The effectiveness of systemic metronidazole – amoxicillin in cases who have DM who have periodontitis was assessed in this systematic review.

Even though the initial search produced 1027 articles, only four have been identified to adhere the investigation's eligibility criteria in their entirety and presenting findings of randomized trials. Three of the investigations that comprised the review compared systemic metronidazole – amoxicillin as an adjunct to scaling & root planning to no management or SRP alone (11, 12, 13). One investigation evaluated systemic metronidazole – amoxicillin with NSD and systemic metronidazole – amoxicillin with operative debridement (14). The bleeding on probing, probing depth, & clinical attachment level, have been all estimated as results in all four investigations.

In cases who are systemically healthy, enhancements in clinical results are related to systemic amoxicillin–metronidazole. It was noted by Sgolastra et al. (16) that the administration of systemic amoxicillin–metronidazole as an adjunct to SRP is related to improved PD decrease & CAL gain. Nevertheless, there was insignificant impact on bleeding on probing and suppuration. The authors determined that chronic periodontitis was effectively treated by amoxicillin–metronidazole as adjuncts to scaling & root planning. Souto et al. (17) conducted a review of eleven trials that utilized various systemic antibiotics, including, amoxicillin with clavulanic a', amoxicillin with metronidazole, azithromycin and doxycycline, as adjuncts to non operative treatments in cases who have diabetes and periodontitis. The effectiveness of doxycycline in conjunction with noninvasive treatment was evaluated in the majority of the trials. Amoxicillin–metronidazole was the most significant factor in the decrease of probing pocket depth. These outcomes are consistent with the findings of our evaluation, which demonstrated that the combination of amoxicillin–metronidazole may enhance periodontal variables.

Mendonca et al. (14) noted that the surgical group experienced a more significant decrease in probing depth & the number of remaining pockets, despite the fact that both non-operative and operative periodontal treatment exhibited a reduction. These

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results were confirmed in non-diabetic individuals by the meta-analysis carried out by Hung et al. (18). The writers observed that surgical periodontal treatments may be more efficient in decreasing probing depth in pockets that were initially deeper. Nevertheless, the attachment gain was comparable among operative and nonoperative treatment (18).

Systemic antibiotics have been recommended for decreasing periodontal pathogenic microflora; however, earlier antimicrobial testing is not always conducted or feasible, resulting in empirical utilize of these therapies, with significant differences in the dosage, period of the prescribed antibiotics and initiation (19). Medical professionals are currently worried about the severe adverse impacts that have been stated and the development of antibiotic resistance, which have been linked to significant death. Antibiotic stewardship programs have been developed by a variety of organizations to mitigate the suboptimal and occasionally unnecessary use of antibiotics (20). Periodontists favor the administration of a combination of amoxicillin–metronidazole because of its extensive spectrum of action and effectiveness against anaerobic organisms (21).

5. Conclusion

This systematic review proposed that the combination of nonsurgical periodontal therapy with systemic amoxicillin–metronidazole may result in superior clinical results. Differences have been noted in the antibiotic prescriptions' durations and dosages, as well as in the therapies administered to the control groups. Cease - reported results for discomfort after therapy, as well as reports of adverse impacts, must be incorporated into future research to guarantee the uniformity of these parameters. It is also important to take into account the possibility of longer duration of monitoring in investigations.

References

- Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of type 2 diabetes mellitus. *Int J Mol Sci.* 2020;21(17):6275.
- Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract.* 2022; 183:109119.
- Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol.* 2018;14(2):88–98.
- Kudiyirickal MG, Pappachan JM. Periodontitis: An often-neglected complication of diabetes. *World J Diabetes.* 2024;15(3):318.
- Stöhr J, Barbaresko J, Neuenschwander M, Schlesinger S. Bidirectional association between periodontal disease and diabetes mellitus: a systematic review and meta-analysis of cohort studies. *Sci Rep.* 2021;11(1):13686.
- Belizário LCG, Figueredo CMS, Rodrigues JVS, Cirelli T, de Molon RS, Garcia VG, Theodoro LH. The Impact of Type 2 Diabetes Mellitus on Non-Surgical Periodontal Treatment: A Non-Randomized Clinical Trial. *J Clin Med.* 2024;13(19):5978.

- Preshaw PM, Bissett SM. Periodontitis and diabetes. *Br Dent J.* 2019;227(7):577–84.
- Pretzl B, Sälzer S, Ehmke B, Schlagenhauf U, Dannewitz B, Dommisch H, Eickholz P, Jockel-Schneider Y. Administration of systemic antibiotics during non-surgical periodontal therapy—A consensus report. *Clin Oral Investig.* 2019; 23:3073–85.
- Dabija-Wolter G, Al-Zubaydi SS, Mohammed MMA, Bakken V, Bolstad AI. The effect of metronidazole plus amoxicillin or metronidazole plus penicillin V on periodontal pathogens in an in vitro biofilm model. *Clin Exp Dent Res.* 2018;4(1):6–12.
- Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR. RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj.* 2019 Aug 28;366.
- El-Makaky Y, Shalaby HK. The effects of non-surgical periodontal therapy on glycemic control in diabetic patients: A randomized controlled trial. *Oral diseases.* 2020 May;26(4):822-9.
- Miranda TS, Feres M, Perez-Chaparro PJ, Faveri M, Figueiredo LC, Tamashiro NS, Bastos MF, Duarte PM. Metronidazole and amoxicillin as adjuncts to scaling and root planing for the treatment of type 2 diabetic subjects with periodontitis: 1-year outcomes of a randomized placebo-controlled clinical trial. *Journal of clinical periodontology.* 2014 Sep;41(9):890-9.
- Gómez-Sandoval JR, Robles-Cervantes JA, Hernández-González SO, Espinel-Bermudez MC, Mariaud-Schmidt R, Martínez-Rodríguez V, Morgado-Castillo KC, Mercado-Sesma AR. Efficacy of clindamycin compared with amoxicillin-metronidazole after a 7-day regimen in the treatment of periodontitis in patients with diabetes: a randomized clinical trial. *BMJ Open Diabetes Research and Care.* 2020 Jan 1;8(1):e000665.
- Mendonça AC, Santos VR, Ribeiro FV, Lima JA, Miranda TS, Feres M, Duarte PM. Surgical and non-surgical therapy with systemic antimicrobials for residual pockets in type 2 diabetics with chronic periodontitis: A pilot study. *Journal of clinical periodontology.* 2012 Apr;39(4):368-76.
- Kolte RA, Kolte AP, Bawankar PV, Bajaj VA. Effect of nonsurgical periodontal therapy on metabolic control and systemic inflammatory markers in patients of type 2 diabetes mellitus with stage III periodontitis. *Contemporary Clinical Dentistry.* 2023 Jan 1;14(1):45-51.
- Sgolastra F, Gatto R, Petrucci A, Monaco A. Effectiveness of systemic amoxicillin/metronidazole as adjunctive therapy to scaling and root planing in the treatment of chronic periodontitis: A systematic review and meta-analysis. *J Periodontol.* 2012;83(10):1257–69.
- Souto MLS, Rovai ES, Ganhito JA, Holzhausen M, Chambrone L, Pannuti CM. Efficacy of systemic antibiotics in nonsurgical periodontal therapy for diabetic subjects: a systematic review and meta-analysis. *Int Dent J.* 2018;68(4):207–20.
- Hung H, Douglass CW. Meta-analysis of the effect of scaling and root planing, surgical treatment and antibiotic therapies on periodontal probing depth and attachment loss. *J Clin Periodontol.* 2002;29(11):975–86.
- Nibali L, Koidou VP, Hamborg T, Donos N. Empirical or microbiologically guided systemic antimicrobials as adjuncts to non-surgical periodontal therapy? A systematic review. *J Clin Periodontol.* 2019;46(10):999–1012.
- Gross AE, Hanna D, Rowan SA, Bleasdale SC, Suda KJ. Successful implementation of an antibiotic stewardship program in an academic dental practice. In: *Open forum infectious diseases.* Oxford University Press US; 2019. p. ofz067.
- Heta S, Robo I. The side effects of the most commonly used group of antibiotics in periodontal treatments. *Med Sci.* 2018;6(1):6.