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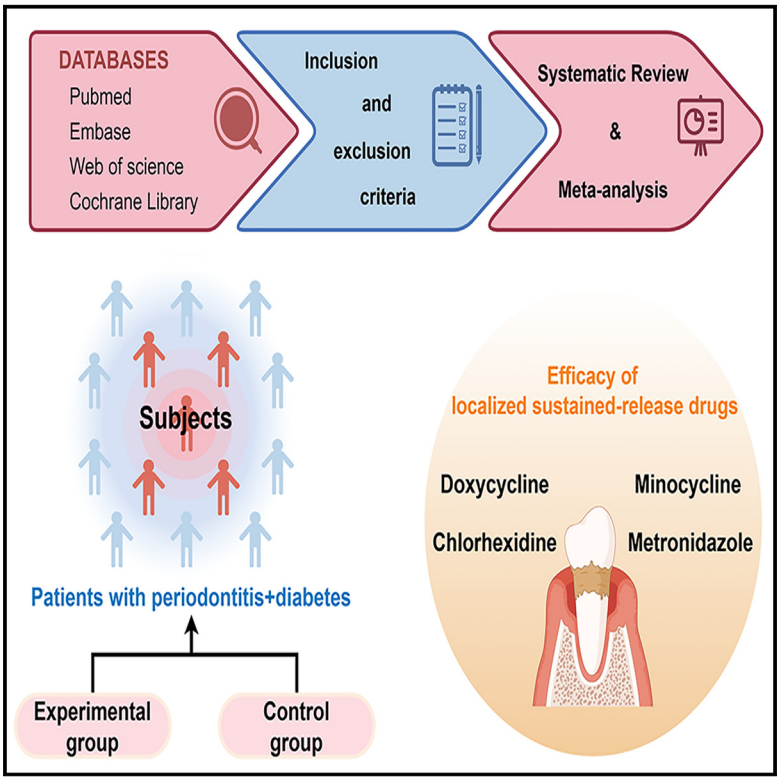
Efficacy of localized sustained-release drugs in periodontitis and comorbid diabetes: A systematic review and meta-analysis

Graphical abstract



Highlights

- Localized sustained-release drugs are significant in periodontal disease treatment
- There is a bidirectional effect between diabetes mellitus and periodontitis
- The efficacy of localized sustained-release drugs in periodontitis + DM is limited

Authors

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In brief

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Efficacy of localized sustained-release drugs in periodontitis and comorbid diabetes: A systematic review and meta-analysis

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SUMMARY

Our meta-analysis aimed to evaluate the efficacy of localized sustained-release drugs in periodontitis and comorbid diabetes. PubMed, Cochrane Library, Embase, and Web of Science were comprehensively searched until 4 December 2024, and 10 randomized controlled trials (RCTs) were included. The results indicated that, compared to the control group, localized sustained-release drugs significantly reduced probing depth (PD) (SMD = −0.77, 95% confidence interval [CI] (−1.37, −0.16)) but did not reduce clinical attachment loss (CAL) (SMD = −0.18, 95% CI (−0.60, 0.23)), sites with glycated hemoglobin (HbA1c) (SMD = 0.03, 95% CI (−0.38, 0.43)), plaque index (SMD = −0.37, 95% CI (−0.80, 0.06)), sites with bleeding on probing (BOP) (SMD = −0.26, 95% CI (−0.68, 0.16)), and gingival index (SMD = 0.07, 95% CI (−0.30, 0.44)). Subgroup analysis by different drugs elicited that, compared to the control treatment, chlorhexidine was effective in reducing BOP% (SMD = −0.55, 95% CI (−0.90, −0.19)). Our meta-analysis finds that the efficacy of localized sustained-release drugs in periodontitis and comorbid diabetes is limited.

INTRODUCTION

Periodontitis is a common disease caused by a multifactorial etiology, and severe periodontitis can lead to loss of periodontal supportive tissues, loosening, and loss of teeth.[1] Periodontitis is characterized by chronic, non-recessive inflammation that is not only confined to the periodontal tissues but also spreads through the vascular system, leading to elevated levels of systemic inflammation.[2] This may have associated effects on other systemic diseases, as well as a profoundly negative impact on patients' daily life. Isola et al.[3] have suggested that periodontitis may have potential negative effects on cardiovascular diseases (CVDs). Smoking, as the most significant risk factor, greatly increases the risk of periodontitis and its severity.[4] Other risk indicators for periodontal diseases cover diabetes mellitus (DM), diseases related to an impaired immune response (like HIV), osteoporosis, malnutrition, medications that contribute to gingival hyperplasia (certain calcium channel blockers, chloramphenicol, and phenytoin sodium), genetic factors (have not yet been clarified), and localized factors (anatomical defects in the alveolar bone).[5] DM, a metabolic chronic disease, has been established as a key risk index for periodontitis.[6] There is a bidirectional effect between DM and periodontitis, with DM enhancing the risk of periodontitis and periodontal inflammation negatively influencing glycemic control.[7] Periodontitis may increase the risk of developing diabetes and negatively affect glycemic control. Research has shown that controlling the inflammatory process of periodontitis may be effective in alleviating diabetes.

In recent years, numerous studies have been conducted regarding periodontitis. A meta-analysis by Polizzi A et al.[8] found that non-surgical periodontal treatment (NSPT) had beneficial effects on flow-mediated dilatation and carotid intima-media thickness, and it could reduce the risk of CVDs in patients with periodontitis. Isola et al.[9] confirmed that NSPT performed with either quadrant-wise subgingival instrumentation or full-mouth subgingival instrumentation was effective in reducing microbial and clinical periodontal parameters.

Current treatment of periodontitis is mainly based on periodontal basic therapy, of which subgingival scaling and root planning (SRP) is the most common,[10] which can effectively reduce periodontal inflammation and alleviate periodontal conditions. However, SRP also has some limitations, such as the difficulty of instruments to completely reach deep and complex periodontal pockets as well as narrow root bifurcations and root surface depressions[11,12] and the inability to remove microbial pathogens located in the dentin tubules.[13] Based on this, there is a need to find new therapeutic tools. Studies have shown that drug therapy is one of the auxiliary means in the clinical treatment of periodontitis, and local

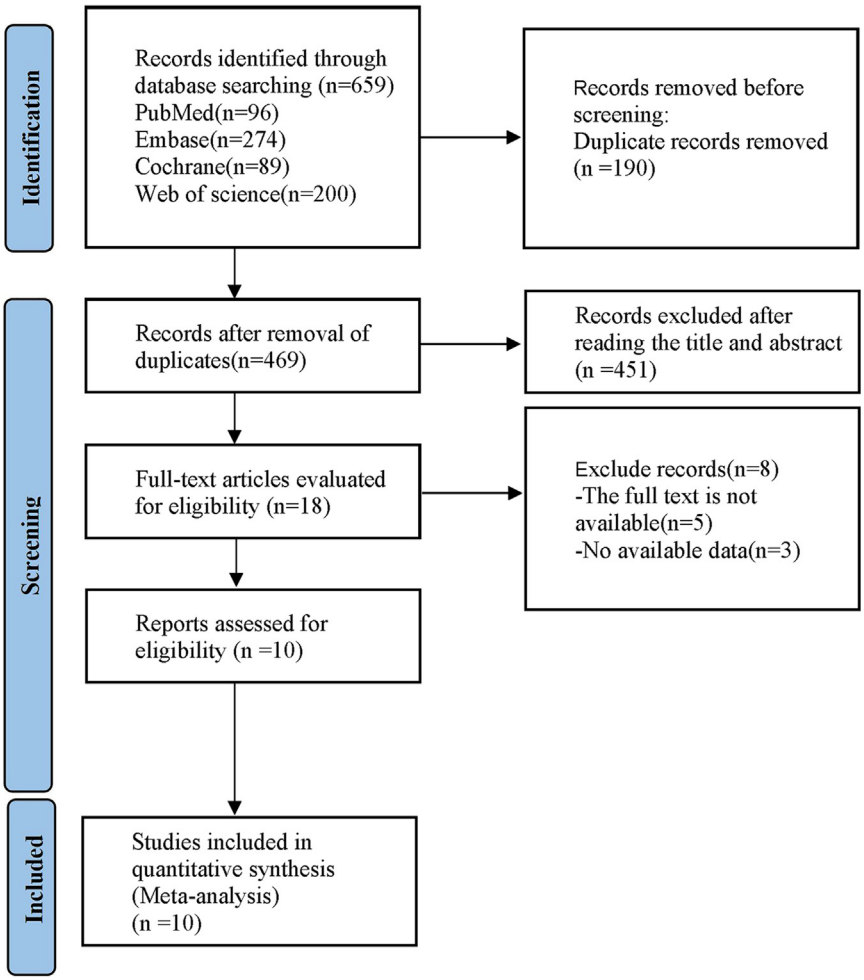

Figure 1. Flowchart of literature search

periodontal medication can effectively avoid many complications caused by systemic medication. Among them, localized sustained-release drugs,[14] with the advantages of small dosage, long duration of action, and not easily producing drug resistance, have become the hotspot of periodontal disease treatment research in recent years. However, the efficacy of different sustained-release drugs is controversial and needs to be further evaluated. Studies[15,16] showed that periodontal parameters like probing depth (PD) were significantly reduced after administration of localized sustained-release drugs, while others[17,18] showed no significant difference in PD compared to the control group. Similarly, contradictory results were reported on other periodontal parameters like clinical attachment loss (CAL), plaque index (PI), gingival index (GI), and bleeding on probing (BOP)% after administration of localized sustained-release drugs. In light of the aforementioned evidence, the present systematic review and meta-analysis aimed to pool evidence on the efficacy of localized sustained-release drugs for patients with periodontitis combined with DM (periodontitis + DM) and provide references for clinical treatment.

RESULTS

Study selection

The flowchart of the selection process is depicted in Figure 1. 659 documents were initially retrieved, of which 190 duplicates were removed and 451 records were deleted after reviewing titles and abstracts. 18 papers were selected for full-text analysis. 5 records were removed because of no available full text, and 3 records were removed because of no available data. Finally, 10 articles were included in this meta-analysis.

Basic characteristics and risk of bias

10 articles[15–17,19–25] were included with 915 patients, with 460 in the experimental group and 455 in the control group. Patients in the experimental group received non-surgical periodontal treatment, basic periodontal treatment, or SRP, along with localized sustained-release drugs (metronidazole, doxycycline, minocycline, and chlorhexidine), while patients in the control group received only non-surgical periodontal treatment, basic periodontal treatment, SRP, localized placebo, or no treatment at all. The follow-up period was 3–6 months. Table 1 lists the basic characteristics. The studies included clearly stated the randomization method used, and the risk of bias is displayed in Figures 2A and 2B. Three randomized controlled trials (RCTs)[15,23,25] were assessed as having a low risk of bias, and one as having some concerns[22] because of bias arising from the randomization process. Six RCTs[16,17,19–21,24] were identified as having a high risk of bias. Bias in outcome measurement was identified as the primary reason for the risk of bias in all six studies.

Result of meta-analysis

Change in PD

As shown in Figure 3A, 9 studies[15–17,20–25] reported the changes in PD after 3 and 6 months of drug treatment, with high heterogeneity (I^2 = 92.1%, p = 0.000). Meta-analysis using a random-effects model unveiled that localized sustained-release drugs significantly reduced PD in periodontitis + DM patients compared to the control group (SMD = −0.77, 95% confidence interval [CI] (−1.37, −0.16), grade: low). Due to the significant heterogeneity, we performed a sensitivity analysis using a leave-one-out method, and the results (Figure S1) showed low sensitivity and stable results for this outcome. Subsequent

Table 1. Baseline characteristics table

Study	Year	Country	Sample size		Gender (M/F)	Mean age		Type of diabetes	Intervention		Outcome	Follow-up time
			EG	CG		EG	CG		EG	CG		
Gilowski	2012	Poland	17	17	16/18	57.6	56	type2 diabetes	doxycycline 20 mg bid for 3 months	placebo	F3; F4; F6	3 months
Chen	2023	China	45	45	NR	NR	NR	type 2 diabetes	minocycline hydrochloride ointment (0.5 g × 5 tubes) for 8 weeks	periodontal basic treatment	F2; F4; F6	3 months
Deo	2010	India	10	10	8/12	37.1	37.1	NR	doxycycline 20-mg capsules twice a day for 6 months	placebo	F1; F2; F5	6 months
Faramarzi	2017	Iran	34	34	NR	52.7	55.3	type 2 diabetes	chlorhexidine gel for 7 days	SRP	F1; F2; F4; F5; F6	6 months
Lecio	2020	Brazil	20	20	14/26	58.6	53.1	type 2 diabetes	20% doxycycline	placebo	F1; F2; F3	6 months
Li	2023	America	21	23	33/11	60.9	66	type 2 diabetes	0.12% chlorhexidine gluconate mouthrinse twice a day for 3 months	SRP	F1; F2; F3; F6	6 months
Martorelli de Lima	2004	Brazil	11	11	4/18	NR	NR	type 1 diabetes	10% doxycycline	placebo	F1; F2	12 months
Michalowicz	2014	America	240	233	253/220	56.8	58.1	type 2 diabetes	chlorhexidine mouth rinse for one month	SRP	F1; F2; F3	6 months
Qureshi	2021	Pakistan	50	50	55/45	52.72	51.24	type 2 diabetes	metronidazole 400 mg × 3 for 10 days	SRP + OHI	F1; F2; F3; F4	3 months
Rathod	2023	India	12	12	13/11	39.53	39.53	type 2 diabetes	1% chlorhexidine gel	triphala gel	F1; F2; F5; F6	6 months

EG, experimental group; CG, control group; M/F, male/female; SRP, scaling and root planing; OHI, oral hygiene instructions; F1: CAL, clinical attachment loss; F2: PD, probing depth; F3: BOP%, bleeding on probing; F4: HbA1c%, glycated hemoglobin; F5: GI, gingival index; F6: PI, plaque index.

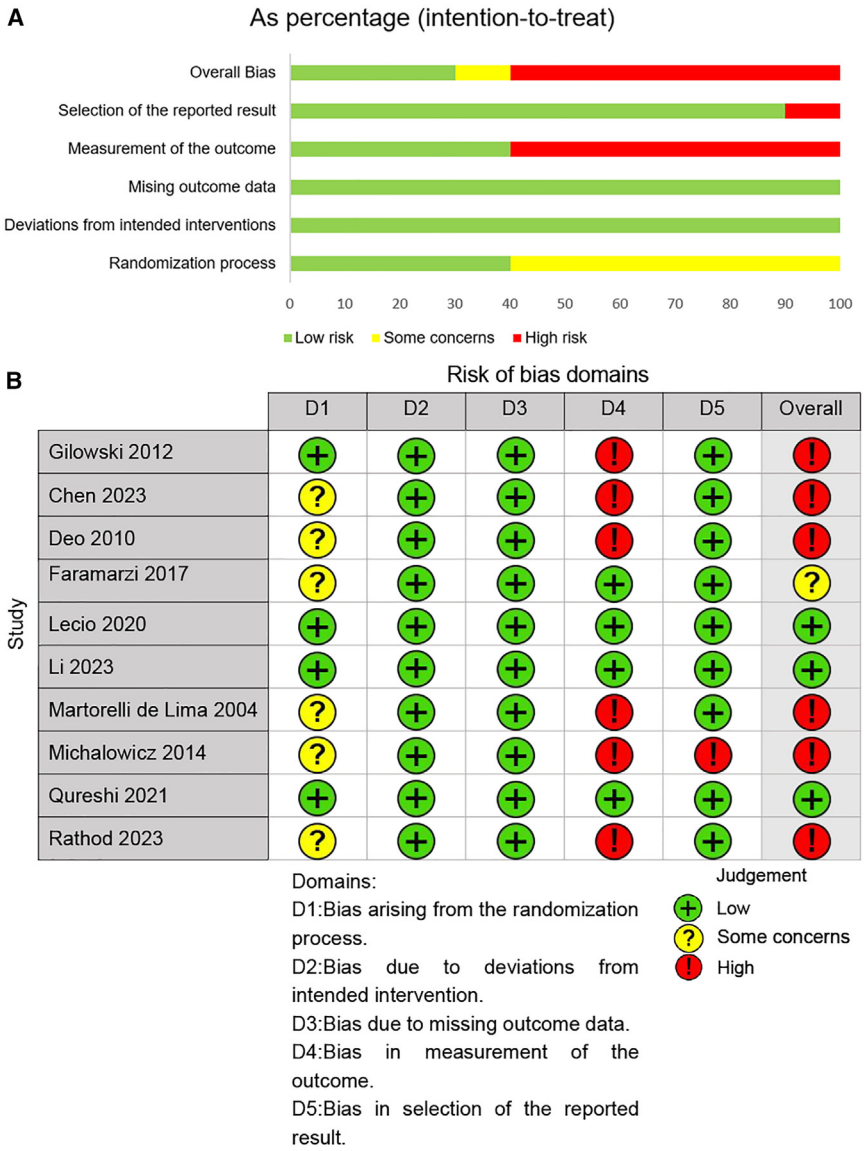

Figure 2. Risk bias

(A) Risk bias of graph; (B) risk bias of summary.

subgroup analysis by different drugs (Figure 3B) elicited that, compared to the control group, doxycycline (SMD = −1.19, 95% CI (−2.87, 0.50)) and chlorhexidine (SMD = −0.09, 95% CI (−0.56, 0.39)) had no significant effect on reducing PD.

Change in PI

As shown in Figure 3C, 5 studies[15,17,19,20,22] reported the change of PI after 3 and 6 months of drug treatment, with high heterogeneity (I^2 = 63.3%, p = 0.028). Meta-analysis using a random-effects model (SMD = −0.37, 95% CI (−0.80, 0.06), grade: low) unveiled that localized sustained-release drugs did not significantly reduce the PI in periodontitis + DM patients after periodontal basal therapy for 3 and 6 months ($p < 0.05$). Due to the significant heterogeneity, a sensitivity analysis was implemented using a leave-one-out method. The results (Figure S2) showed low sensitivity and stable results for this outcome. Subgroup analyses by different drugs (Figure 3D) showed that, compared to the control group, chlorhexidine (SMD = −0.22, 95% CI (−0.57, 0.12)) did not notably affect PI.

Change in CAL

As shown in Figure 4A, 8 studies[15–17,21–25] reported the change of CAL after 3 and 6 months of drug treatment, with high heterogeneity (I^2 = 80.4%, p = 0.000). Meta-analysis using a random-effects model (SMD = −0.18, 95% CI (−0.60, 0.23), grade: low) revealed that localized sustained-release drugs did not significantly reduce CAL of periodontitis + DM patients after periodontal basal therapy for 3 and 6 months ($p < 0.05$). Due to the significant heterogeneity, a sensitivity analysis was implemented using a leave-one-out method. The results (Figure S3) showed low sensitivity and stable results for this outcome.

Subgroup analyses by different drugs (Figure 4B) showed that, compared to the control group, doxycycline (SMD = −1.08, 95% CI (−2.32, 0.17)) and chlorhexidine (SMD = −0.06, 95% CI (−0.37, 0.26)) did not have a significant effect in reducing CAL of patients after 3 and 6 months.

Change in BOP%

As shown in Figure 4C, 5 studies[15,19,23–25] reported the change of BOP% after 3 and 6 months of drug treatment, with high heterogeneity (I^2 = 77.9%, p = 0.001). Meta-analysis using a random-effects model (SMD = −0.26, 95% CI (−0.68, 0.16), grade: low) indicated that localized sustained-release drugs could not significantly reduce BOP% in periodontitis + DM patients after periodontal basal therapy for 3 and 6 months ($p < 0.05$). Due to the significant heterogeneity, a sensitivity analysis was implemented using a leave-one-out method. The results (Figure S4) showed low sensitivity and stable results for this outcome.

Subgroup analyses by different drugs (Figure 4D) signaled that, compared to the control group, chlorhexidine (SMD = −0.55, 95% CI (−0.90, −0.19)) was effective in reducing BOP% in patients after 3 and 6 months, while doxycycline (SMD = −0.26, 95% CI (−0.98, 0.47)) did not have a significant effect.

Change in GI

As shown in Figure 5A, 3 studies[17,21,22] reported the change of GI after 3 and 6 months of drug treatment, with no heterogeneity (I^2 = 0.0%, p = 0.670). Meta-analysis using a fixed-effects model (SMD = 0.07, 95% CI (−0.30, 0.44), grade: moderate) showed that localized sustained-release drugs could not significantly

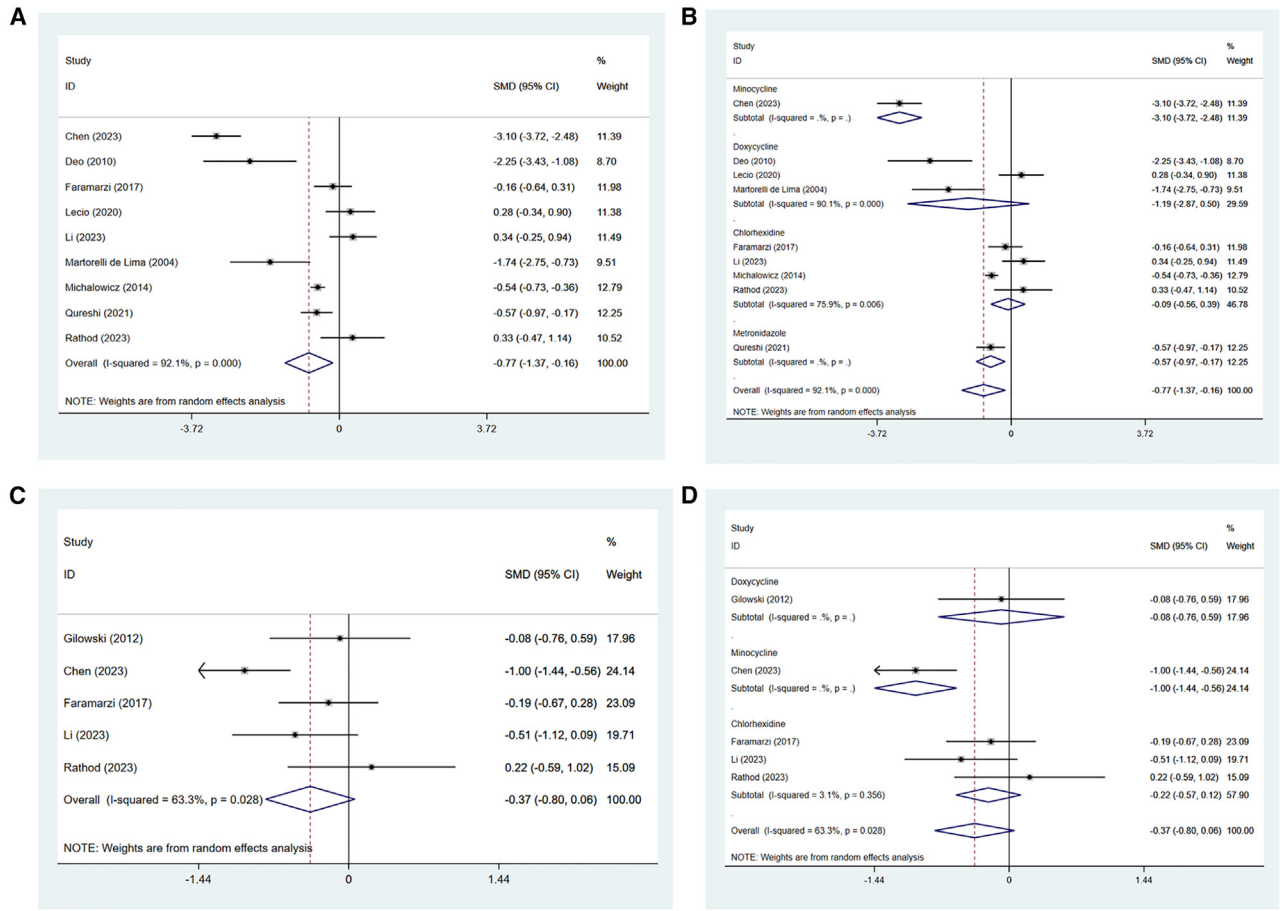

Figure 3. Forest plot

(A) Forest plot of meta-analysis of change in PD; (B) forest plot of meta-analysis of subgroup change in PD; (C) forest plot of meta-analysis of change in PI; (D) forest plot of meta-analysis of subgroup change in PI. Data are represented as SMD (95% CI).

reduce GI in periodontitis + DM patients after periodontal basal therapy for 3 and 6 months ($p > 0.05$).

Subgroup analyses by different drugs (Figure 5B) showed that, compared to the control group, chlorhexidine (SMD = 0.15, 95% CI (−0.26, 0.56)) did not have a marked effect on GI in patients after 3 and 6 months.

Change in HbA1c%

As shown in Figure 5C, 4 studies[19,20,22,25] reported the change of HbA1c% after 3 and 6 months of drug treatment, with high heterogeneity (I^2 = 65.5%, p = 0.033). Due to high heterogeneity, meta-analysis using a random-effects model (SMD = 0.03, 95% CI (−0.38, 0.43), grade: low) showed that localized sustained-release drugs did not significantly reduce HbA1c% in periodontitis + DM patients after periodontal basal therapy for 3 and 6 months ($p < 0.05$). Due to the significant heterogeneity, a sensitivity analysis was implemented using a leave-one-out method. The results (Figure S5) showed low sensitivity and stable results for this outcome.

Adverse events

Heterogeneity was assessed by observing the treatment effect plots and their 95% CIs and testing for heterogeneity before meta-analysis. In this study, changes in PD, PI, CAL, BOP%, GI%, and HbA1c% between the experimental group and the control group at 3- and 6-month post-treatment follow-up were tallied. To further determine the source of heterogeneity, sensitivity analyses of the included indicators were performed. Due to the notable heterogeneity, we performed a meta-analysis by the leave-one-out method, and the results were unchanged, indicating that the systematic evaluation of the corresponding effect sizes was stable, and the results were reliable. The significant heterogeneity may be related to the small sample size of included studies and the inconsistency of the baseline periodontal level of the included studies. Meta-analysis was performed using a random-effects model to correct for the heterogeneity and make the results more reliable.

Publication bias

Publication bias was appraised by performing Egger's test for changes in PD, PI, CAL, BOP%, GI, and HbA1c%. The results showed publication bias in PD (p = 0.000), PI (p = 0.028), CAL (p = 0.000), BOP% (p = 0.001), and HbA1c% (p = 0.033), except for GI (p = 0.670) (Figures S6–S11).

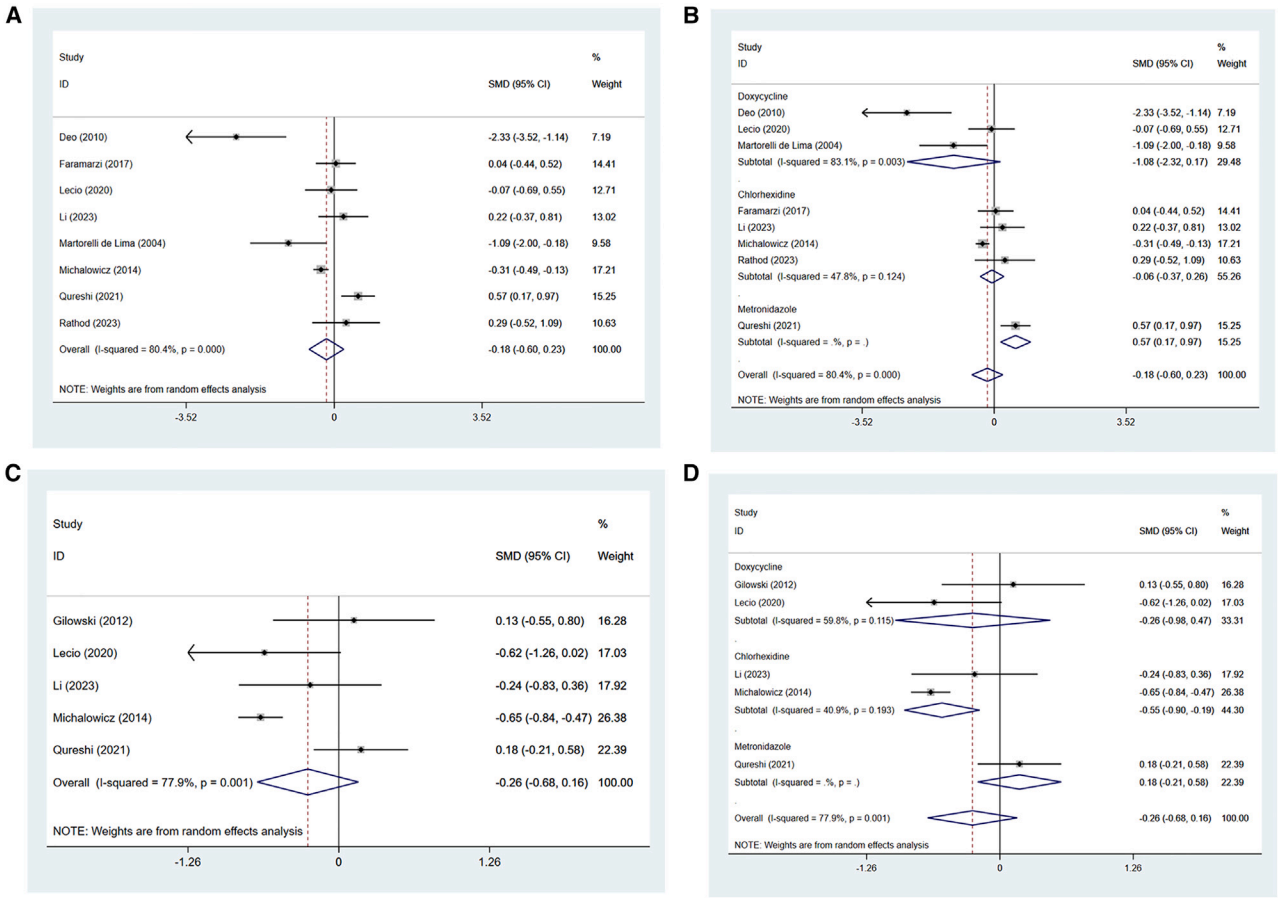

Figure 4. Forest plot

(A) Forest plot of meta-analysis of change in CAL; (B) forest plot of meta-analysis of subgroup change in CAL; (C) forest plot of meta-analysis of change in percentage of BOP; (D) forest plot of meta-analysis of subgroup change in percentage of BOP. Data are represented as SMD (95% CI).

DISCUSSION

Patients with periodontitis + DM may have problems in chewing and digestion with poor general conditions, which negatively affect life and social activities, as well as mental health. Therefore, it is crucial to find effective treatments to improve the physical and mental health and the quality of life of patients with periodontitis + DM.

This study is the first meta-analysis using an evidence-based medicine approach to assess the efficacy of localized sustained-release drugs in periodontitis + DM patients. 10 RCTs were included, and the results illustrated that localized sustained-release drugs significantly reduced PD in periodontitis + DM patients after 3 and 6 months but did not significantly reduce PI, CAL, BOP%, GI, and Hba1c%. Considering the effect of drug types on the results, subgroup analyses were conducted for different drugs to assess various periodontal and protein indicators after 3 and 6 months of treatment. Chlorhexidine was effective in reducing BOP% in patients, while others were not effective. However, considering the high heterogeneity and the risk of bias of the included studies, the results cannot fully substantiate the efficacy of localized sustained-release drugs in patients with periodontitis + DM.

Metronidazole

Metronidazole sustained-release agent is a nitroimidazole drug that causes bacterial death through reduction of nitro by anaerobic bacteria, production of cytotoxic substances, or inhibition of deoxyribonucleic acid synthesis in sensitive bacteria.[26] In clinical applications, it can be categorized into metronidazole gel, ethyl cellulose film, and acrylic strips. The use of metronidazole to improve clinical outcomes in patients with chronic periodontitis has been widely recognized, but its effectiveness is limited to periodontal pathogens and is ineffective against inflammatory periodontal damage. The study by Qureshi[27] included in this paper uncovered that metronidazole only reduced PD in patients and may not have a significant effect on periodontitis + DM.

Cruz et al.[28] found that diabetic patients treated with metronidazole plus amoxicillin-assisted SRP maintained their condition better than patients treated with SRP only for 5 years. However, Jansson et al.[27] did not find any notable clinical and microbiological differences between patients with recurrent periodontitis

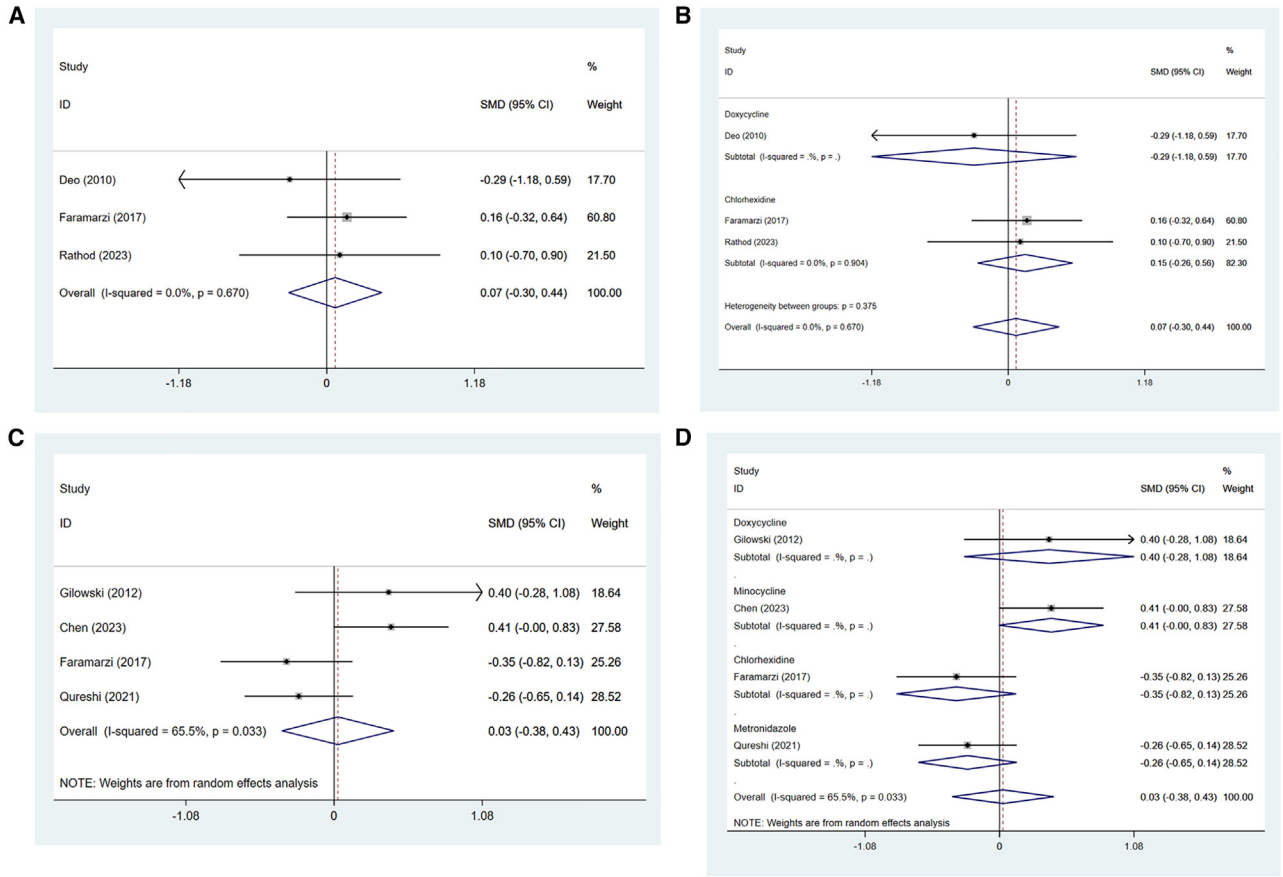

Figure 5. Forest plot

(A) Forest plot of meta-analysis of change in GI; (B) forest plot of meta-analysis of subgroup change in GI; (C) forest plot of meta-analysis of change in percentage of HbA1c; (D) forest plot of meta-analysis of subgroup change in percentage of HbA1c. Data are represented as SMD (95% CI).

treated with localized metronidazole gel and placebo gel, which was consistent with our results.

Minocycline

As a broad-spectrum antibiotic, minocycline can effectively inhibit pathogenic bacteria in periodontal tissues and eliminate periodontal pathogens.[18] Minocycline hydrochloride has a high affinity for bone tissue, inhibits collagenase activity, inhibits bone resorption, promotes fibroblast attachment, and reduces damage to periodontal tissues, thus promoting periodontal tissue regeneration.[29] Therefore, minocycline may have certain efficacy for treating periodontitis. Currently, minocycline sustained-release formulations include minocycline gel, sustained-release film, and microspheres. Lin et al.[30] found that non-surgical periodontal treatment with subgingival application of minocycline significantly improved periodontal status and moderately improved HbA1c. Ren et al.[31] used semiconductor laser-assisted minocycline therapy and minocycline injections alone to treat patients with chronic periodontitis combined with type 2 diabetes mellitus (T2DM) and obesity. The results unraveled marked improvement ($p < 0.05$) in bleeding amount on probing, GI, PD, PI, CAL, and gingival sulcus bleeding index in both groups after treatment (12 weeks). This was consistent with the finding of Chen et al.[15] that minocycline could effectively reduce PD and PI.

Doxycycline

Doxycycline is one of the common tetracycline drugs. In clinical applications, it has the advantages of a broad antibacterial spectrum and strong bacteriostatic effect. It is similar to tetracycline in application, but the effect is more obvious. Doxycycline inhibits metalloproteinase activity and has an antibacterial effect, which helps to reduce periodontal tissue inflammation.[32] Other common doxycycline sustained-release agents used in clinical practice include injections, microspheres, and *in situ* gels. Our present study illustrated that doxycycline was not effective in reducing periodontitis-related markers. Grossi et al. showed in 1997 that patients treated with doxycycline had a reduction in HbA1c at the 3-month follow-up.[33] Ronaldo et al.[34] evinced that the addition of doxycycline to SRP periodontal therapy did not notably improve metabolic control in patients with periodontitis. These results were in line with our findings.

Chlorhexidine

Chlorhexidine is a broad-spectrum antimicrobial agent. In clinical application, it has strong bactericidal effects on

gram-positive bacteria, gram-negative bacteria, and various fungi. Chlorhexidine sustained-release agents can be divided into tablets, gels, and compound emulsions. After years of clinical research, chlorhexidine is recognized as the gold-standard drug against plaque and gingivitis. The antiplaque effect of chlorhexidine is a result of the dioxide nature of the chlorhexidine molecule, which gives the agent a long-lasting antimicrobial effect on the tooth surface through bactericidal and bacteriostatic actions.[35] Almeida et al.[36] applied chlorhexidine digluconate (CHX) gel in a whole-mouth disinfection protocol in patients with periodontitis combined with DM, which improved all clinical parameters of patients. Cosyn et al.[37] applied chlorhexidine varnish as an adjunct to SRP for chronic periodontitis and showed a substantial reduction in PD and CAL ($p < 0.001$), which was highly efficacious. They also found that the combination of mechanical debridement and repeated use of chlorhexidine chips significantly improved the rate of cavity reduction and clinical attachment compared to SRP alone.[38] However, this study found that chlorhexidine had no significant effect on reducing PD, PI, CAL, GI, and HbA1c% but could successfully reduce BOP%.

Strengths of the study

This study has several strengths. First, this is the first meta-analysis to examine the efficacy of localized sustained-release drugs in patients with periodontitis and comorbid diabetes, which can provide a rigorous theoretical basis for clinical treatment. Second, only high-quality RCTs were included in our study, which ensured the accuracy and rigor of the findings.

Limitations of the study

There are several limitations: (1) enrolled literature is limited, and the follow-up period is short; (2) only English-language literature was searched, so literature published in other languages may be missed; and (3) significant heterogeneity and publication bias existed.

Conclusion

In conclusion, the efficacy of localized sustained-release drugs in patients with periodontitis combined with DM at 3 and 6 months is limited. When formulating a therapeutic strategy for patients with periodontitis and comorbid diabetes, it is essential to consider the appropriate dosage and administration of localized sustained-release drugs, as well as the potential adverse effects. A combination of systemic medications or other methods is needed. However, the results are limited due to the few included articles and a small clinical sample size. More RCTs with large samples, multi-center, high quality, and longer follow-up duration are needed to confirm the findings and to search for more reliable and relevant evidence.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Rongquan Duan (RongquanD@xzhmu.edu.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data reported in this paper will be shared by the lead contact upon request.
- All original code has been deposited at Mendeley Data and is publicly available as of the date of publication. DOIs are listed in the key resources table.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Writing – original draft preparation: J.Z.; writing – review and editing: J.Z.; conceptualization: Y.R. and M.Y.; methodology: J.Z. and M.C.; formal analysis and investigation: R.D.; funding acquisition: R.D.; resources: R.D. and C.Y.; supervision: R.D. and C.Y. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Raw data and original code	This paper	Mendeley Data, https://doi.org/10.17632/npnhbbr3mf.1
Software and algorithms		
EndNote X9.1	Thomson Scientific	https://endnote.com/downloads
STATA SE15.0	Stata Corp LLC	https://www.stata.com/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

The study did not use experimental models typical in the life sciences.

METHOD DETAILS

Data sources

The protocol was approved and registered in the PROSPERO (CRD42024507025). The review was reported following the guidelines from the Cochrane Handbook[39] and the PRISMA statement.[40]

The Graded Recommendations Assessment Development and Evaluation (GRADE) system was utilized to evaluate the evidence for methodological quality. Five factors that could reduce the quality of evidence were considered, including study limitations, inconsistent findings, inconclusive direct evidence, inaccurate or wide confidence intervals, and publication bias. In addition, three factors that could reduce the quality of evidence were reviewed, including effect size, possible confounding factors, and dose-effect relationships. A comprehensive description of the quality of evidence for each parameter data is provided in the Table S1.

Study selection

Inclusion and exclusion criteria

According to the Participant, Intervention, Comparison, Outcome, and Study (PICOS) guidelines,[41] the inclusion and exclusion criteria were set as follows:

Inclusion criteria:

(1) Participants: (1) patients diagnosed with periodontitis+DM (T1DM or T2DM); (2) not taking antibacterial or non-steroidal anti-inflammatory drugs over the past 3 months.
(2) Intervention: patients in the intervention group received localized sustained-release preparations (metronidazole, minocycline, doxycycline, chlorhexidine).
(3) Comparison: patients in the control group received basic periodontal treatment (supragingival scaling, SRP) or no treatment.
(4) Outcomes: Primary outcomes: probing depth (PD), plaque index (PI), clinical attachment loss (CAL), site with bleeding on probing (BOP), and gingival index (GI).
Secondary outcomes: site with glycated hemoglobin (HbA1c).
(5) Study: Published randomized controlled trials (RCTs).

Exclusion criteria: (1) Conference abstracts, meta-analyses, systematic reviews, animal experiments, case reports, and studies with unavailable full text. (2) Use of medications other than localized sustained-release drugs during participation in the study. (3) Studies with less than 1 month of follow-up. (4) Non-English literature.

Literature retrieval

RCTs on localized sustained-release drugs in periodontitis combined with diabetes mellitus were searched in PubMed, Cochrane Library, Embase, and Web of Science up to 4 December 2024, using the Mesh words combined with free words: Periodontitis, Diabetes Mellitus, Metronidazole, Tetracycline, Minocycline, Doxycycline, Chlorhexidine. Detailed search strategies are provided in Data S1.

Data extraction

Two reviewers reviewed the titles, abstracts, and the full text of studies meeting the inclusion criteria. Any disagreement was resolved through discussion or seeking the opinion of a third party to negotiate and reach a consensus. Information extracted from the

included studies included authors, year, country, sample size (test and control groups), sex (male/female), mean age, type of diabetes, intervention, and outcomes. All data in Excel were reviewed to consider appropriateness for meta-analysis. Data were then imported into StataSE15.0 for quantitative analysis.

Risk of bias of the included studies

The risk of bias was rated independently by two investigators using Cochrane's Risk of Bias 2 Tool (RoB 2).[42] Any disagreement was addressed by consulting a third person to reach a consensus. Five domains were assessed, including the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. Every single domain was evaluated as having a low risk of bias, some concerns, or a high risk of bias. The overall assessment of each article was concluded as follows: "low risk of bias" if all domains were assessed as a low risk of bias; "some concerns" if at least one domain was evaluated as some concerns and no domain was assessed as high risk; "high risk of bias" if at least one or more domains were assessed as a high risk of bias. The publication bias was appraised using Egger's test for primary outcomes.

QUANTIFICATION AND STATISTICAL ANALYSIS

The collected data were statistically analyzed using StataSE15.0 (Stata Corp, College Station, TX, USA). Continuous variables were depicted as standardized mean difference (SMD) and 95% confidence interval (CI), while dichotomous variables were depicted as odds ratio (OR) and 95% CI. Heterogeneity across studies was judged using I^2 values and Q statistics. If the $I^2 \geq 50\%$ and $p < 0.05$, a random-effects model was used to pool the results, and sensitivity analysis and subgroup analysis were implemented to explore the potential source of heterogeneity. If $I^2 < 50\%$ and $p > 0.05$, analyses were implemented using a fixed-effects model. In addition, the funnel plot and Egger's test were used to test publication bias.