ISSN 0973-2063 (online) 0973-8894 (print)

Bioinformation 22(8): 5480-5485 (2026)

BIOINFORMATION
Discovery at the interface of physical and biological sciences

BIOMEDICAL INFORMATICS

www.bioinformation.net

Volume 22(8)

Research Article

Received August 1, 2026; Revised August 31, 2026; Accepted August 31, 2026, Published August 31, 2026

DOI: 10.6026/973206300225480

SJIF 2026 (Scientific Journal Impact Factor for 2026) = 8.478
2022 Impact Factor (2023 Clarivate Inc. release) is 1.9

Edited by Hiroj Bagde
E-mail: hirojbagde8@gmail.com
Phone: +91 9766105900
Citation: Ranjan *et al.* Bioinformation 22(8): 5480-5485 (2026)

Metformin and nano-metformin gels as adjuncts to periodontal therapy: A split-mouth trial

Rohit Ranjan[1], B.J. Janardhana Amaranath[1,*], Shikha Verma[1], Koushik Mukherjee[2], Utkarsh Singh[1] & Amit Yadav[1]

[1]Department of Periodontology, Rama Dental College Hospital & Research Centre, Rama University, Mandhana, Kanpur, Uttar Pradesh, India; [2]Department of Periodontology, Guru Nanak Institute of Dental Sciences and Research, Kolkata, West Bengal, India; *Corresponding author

Affiliation URL:
https://www.ramadentalcollege.com/
https://www.gnidsr.ac.in/

ISSN 0973-2063 (online) 0973-8894 (print)
Bioinformation 22(8): 5480-5485 (2026)

Author contact:
Rohit Ranjan - E-mail: drrohitperio2611@gmail.com; Phone: +91 8987249650
B.J. Janardhana Amaranath - E-mail: dramarbj@gmail.com
Shikha Verma - E-mail: vermashikha544@gmail.com
Koushik Mukherjee - E-mail: mukherjeedrkoushik@gmail.com
Utkarsh Singh - E-mail: drutkarshsinghsurgeon@gmail.com
Amit Yadav - E-mail: ay29jan92@gmail.com

Abstract:
Chronic periodontitis produces persistent periodontal inflammation, pocket formation, attachment loss and intrabony defects, while scaling and root planing alone may have limited access in deep and anatomically complex sites. Thirty systemically healthy participants contributed 90 intrabony defect sites in a split-mouth randomized design allocated to SRP with placebo gel, SRP with 1% metformin gel, or SRP with 1% nano-metformin gel; plaque index, gingival index, probing pocket depth and clinical attachment level were recorded at baseline, 1 month and 3 months and radiographic intrabony defect depth at baseline and 6 months. Plaque reduction was comparable among groups, whereas gingival inflammation, pocket depth, attachment level and radiographic defect depth improved significantly more with metformin-containing gels. The greatest improvements were observed with 1% nano-metformin, with mean reductions of 3.20 ± 0.49 mm in probing depth, 2.78 ± 0.68 mm in clinical attachment level and 2.35 ± 0.38 mm in intrabony defect depth. Thus, subgingival 1% metformin gel enhanced the effect of scaling and root planing and nano-metformin provided superior clinical and radiographic outcomes, suggesting a promising locally delivered regenerative adjunct for chronic periodontitis.

Keywords: Chronic periodontitis, local drug delivery, metformin, nano-metformin, scaling and root planing, intrabony defect

Background:
Periodontitis is a biofilm-associated inflammatory disease in which dysbiotic subgingival communities and an excessive host response lead to destruction of periodontal ligament, cementum and alveolar bone. Contemporary classification systems emphasize that the disease should be understood not only by clinical attachment loss and bone loss but also by complexity, rate of progression and risk profile **[1]**. Its pathogenesis involves a sustained interaction between microbial challenge and immune-inflammatory mediators and the clinical expression ranges from localized pocketing to advanced tooth-support loss. The public health importance of periodontitis remains substantial **[2]**. Recent epidemiological evidence indicates that periodontitis affects a large proportion of dentate adults globally, with severe forms contributing to tooth loss, impaired oral function and wider health burden **[3]**. The tissue destruction is not a simple direct effect of bacteria; rather, microbial dysbiosis triggers innate and adaptive immune pathways, cytokine release, matrix metalloproteinase activity, osteoclastogenesis and inflammatory bone resorption. For this reason, successful periodontal therapy requires both reduction of the microbial load and control of the inflammatory environment that drives connective tissue and bone breakdown **[4]**. Scaling and root planing is the cornerstone of non-surgical periodontal therapy and is recommended as a primary intervention in stepwise management of periodontitis. Mechanical debridement disrupts subgingival biofilm and calculus, improves gingival health and reduces periodontal pocket depth **[5]**. However, root morphology, deep pockets, furcation involvement, grooves, patient-related factors and incomplete access may limit complete removal of pathogenic biofilm **[6]**. Systematic evaluations have shown that non-surgical therapy is effective, but the magnitude of improvement may vary, especially in deeper defects and sites with unfavorable anatomy **[7]**. Systemic antimicrobials may enhance outcomes in selected situations, but concerns related to resistance, adverse effects and unnecessary systemic exposure support a cautious and restricted approach. Local drug delivery provides an attractive alternative because the therapeutic agent is placed directly into the periodontal pocket, where it can maintain a high local concentration with minimal systemic burden **[8]**. Professionally delivered local adjuncts may be useful in persistent or isolated sites that do not respond adequately to mechanical instrumentation alone **[9]**. Modern drug delivery concepts further emphasize biomaterials, controlled release systems and nanoparticle carriers to improve retention, tissue penetration and biological activity within periodontal defects. Metformin is a biguanide drug widely used for type 2 diabetes mellitus, but its periodontal interest arises from anti-inflammatory, antioxidant, osteogenic and osteoclast-modulating actions **[10]**. Clinical trials using subgingivally delivered metformin gel have reported favorable reductions in probing depth, gains in clinical attachment and improvement in intrabony defect fill when used with scaling and root planing **[11, 12]**. Additional controlled studies have shown that 1% metformin gel can improve outcomes in intrabony defects and in moderate to severe chronic periodontitis **[13, 14]**. Evidence synthesis has also suggested that locally delivered metformin produces better bone defect fill and periodontal parameter improvement than scaling and root planing alone **[15]**. Experimental evidence supports these clinical observations. Metformin has been shown to reduce alveolar bone destruction in ligature-induced periodontitis and to modify markers related to inflammation and bone metabolism **[16]**. It can also decrease

oxidative stress, inflammatory mediators and bone loss in periodontal models, supporting its use as a host-modulatory and regenerative adjunct **[17]**. Nanoparticle-based delivery systems may further improve drug dispersion, bioavailability, sustained release and access to difficult periodontal microenvironments. Nevertheless, clinical information on nano-metformin as a local periodontal adjunct is limited **[18]**. Therefore, it is of interest to evaluate and compare the clinical efficacy of 1% metformin gel and 1% nano-metformin gel following subgingival application as adjuncts to scaling and root planing and to assess the residual interdental bone levels radiographically in intrabony defects associated with chronic periodontitis.

Materials and Methods:

Study design and setting:

This split-mouth, site-level, randomized, placebo-controlled clinical study was conducted in the Department of Periodontology, Rama Dental College Hospital and Research Centre, Kanpur, Uttar Pradesh, India, over a 12-month period. The study protocol was approved by the institutional ethics committee. The purpose and procedure were explained to all eligible participants and written informed consent was obtained before enrollment.

Sample size and participants:

The sample size was calculated for 90% power and 5% type I error using expected variation in intrabony defect depth reduction. A total of 30 systemically healthy participants, comprising 15 males and 15 females aged 25-60 years, were recruited from the outpatient department. Each participant contributed three qualifying periodontal sites from three different quadrants, resulting in 90 study sites.

Inclusion criteria:

Participants were included if they were 25-60 years of age, systemically healthy and presented with periodontal sites having probing pocket depth of at least 5 mm, clinical attachment level of at least 4 mm and radiographic vertical bone loss of at least 3 mm. Each participant was required to have one eligible intrabony defect site in at least three different quadrants to permit a split-mouth allocation.

Exclusion criteria:

Patients were excluded if they had received periodontal therapy or antibiotics during the preceding 6 months, were taking systemic metformin or any oral antidiabetic medication, used tobacco, consumed alcohol regularly, had substance abuse history, were pregnant or lactating, had systemic disease or immunocompromised status, were unwilling to comply with the protocol, or had known allergy to metformin or biguanide-related drugs.

Randomization and interventions:

Three eligible sites in each participant were randomly allocated by lottery method to one of three treatment groups. Group I received scaling and root planing with placebo gel, Group II received scaling and root planing with 1% metformin gel and Group III received scaling and root planing with 1% nano-metformin gel. Full-mouth scaling and root planing was performed using an ultrasonic scaler and Gracey curettes. The allocated gel was delivered sub-gingivally into the selected site, followed by placement of periodontal dressing to aid retention.

Gel preparation:

A gellan gum-based gel vehicle was used for placebo and active formulations. The placebo gel was prepared using gellan gum dispersed in distilled water with mannitol, sucralose, citric acid, methylparaben, propylparaben and sodium citrate. For the 1% metformin formulation, metformin was incorporated into the same gel base. The 1% nano-metformin gel was prepared by homogenizing the metformin gel under high-pressure conditions for 3-4 hours to obtain a nano-formulated preparation.

Clinical and radiographic measurements:

Plaque index was recorded using an explorer, while gingival index, probing pocket depth and clinical attachment level were recorded using a UNC-15 periodontal probe with a customized acrylic stent to standardize probe positioning. Clinical parameters were measured at baseline, 1 month and 3 months. Digital intraoral periapical radiographs were obtained using a long cone paralleling technique at baseline and 6 months. Intrabony defect depth was calculated as the distance from the cemento-enamel junction to the base of the defect minus the distance from the cemento-enamel junction to the alveolar crest.

Post-operative instructions and follow-up:

Participants were advised not to rinse forcefully or spit for 24 hours and to avoid brushing, flossing, or using interdental aids at treated sites during the immediate postoperative period. The periodontal dressing was removed after 1 week and participants were instructed to resume toothbrushing with a soft-bristled toothbrush using the Modified Bass technique. Medicated mouth rinses were discouraged to avoid confounding of local effects.

Statistical analysis:

Data were analyzed using SPSS and Microsoft Excel. Continuous variables were expressed as mean ± standard deviation, while categorical variables were expressed as frequency and percentage. Intergroup comparisons were performed using one-way analysis of variance and repeated-measures analysis was used for within-group changes over time. A p-value less than 0.05 was considered statistically significant.

Results:

Thirty participants completed the study and all 90 allocated sites were available for analysis. Each group contained 30 sites because every participant contributed one site to the placebo group, one site to the 1% metformin group and one site to the 1% nano-metformin group. Baseline probing pocket depth, clinical attachment level and intrabony defect depth were comparable among the three groups, confirming adequate site-level balance for the principal clinical and radiographic outcomes. Gingival

index showed baseline variation, with the nano-metformin sites having higher initial inflammation; this was considered during interpretation because the same group still achieved the lowest follow-up gingival scores. Plaque index decreased substantially in all three groups, but the magnitude of plaque reduction was similar. Mean plaque index reduced from 2.65 ± 0.24 to 0.90 ± 0.15 in the placebo group, from 2.69 ± 0.16 to 0.91 ± 0.18 in the 1% metformin group and from 2.63 ± 0.21 to 0.90 ± 0.21 in the 1% nano-metformin group. The change scores were not statistically different among groups, indicating that plaque control was mainly attributable to scaling and root planing with oral hygiene reinforcement rather than the specific gel used. Gingival index showed a clear graduated improvement. At 3 months, the mean score was 1.00 ± 0.23 in the placebo group, 0.80 ± 0.24 in the 1% metformin group and 0.60 ± 0.19 in the 1% nano-metformin group. The mean gingival index reduction was 1.11 ± 0.27, 1.39 ± 0.25 and 1.73 ± 0.22, respectively and the intergroup difference was statistically significant. This suggests a stronger anti-inflammatory response in sites receiving metformin, particularly in the nano-metformin group. Probing pocket depth and clinical attachment level improved in all groups, but the improvements were greatest with nano-metformin. Probing pocket depth reduced from 7.17 ± 0.47 mm to 3.97 ± 0.33 mm in the nano-metformin group, compared with final values of 4.49 ± 0.42 mm in the metformin group and 5.35 ± 0.45 mm in the placebo group. Clinical attachment level improved from 6.08 ± 0.60 mm to 3.30 ± 0.62 mm in the nano-metformin group, compared with 3.90 ± 0.67 mm in the metformin group and 4.80 ± 0.65 mm in the placebo group. Radiographic assessment at 6 months showed significant intrabony defect depth reduction in all groups. The placebo group showed a mean reduction of 0.84 ± 0.48 mm, the 1% metformin group showed 1.87 ± 0.45 mm and the 1% nano-metformin group showed 2.35 ± 0.38 mm. The final intrabony defect depth was lowest in the nano-metformin group, indicating superior radiographic bone fill. Intergroup comparisons of change scores were statistically significant for gingival index, probing pocket depth, clinical attachment level and intrabony defect depth, but not for plaque index. Baseline site comparability, longitudinal clinical outcomes and radiographic/intergroup change outcomes are presented in **Tables 1, 2 and 3** respectively.

Table 1: Study site distribution and baseline comparability

Variable	Placebo (SRP + placebo)	1% Metformin (SRP + MF)	1% Nano-metformin (SRP + Nano-MF)	p-value
Study sites, n	30	30	30	-
Participants contributing sites	30	30	30	-
Plaque Index	2.65 ± 0.24	2.69 ± 0.16	2.63 ± 0.21	0.519
Gingival Index	2.11 ± 0.20	2.19 ± 0.17	2.33 ± 0.16	<0.001
PPD (mm)	7.15 ± 0.49	7.19 ± 0.52	7.17 ± 0.47	0.953
CAL (mm)	6.06 ± 0.47	6.09 ± 0.59	6.08 ± 0.60	0.976
IBD depth (mm)	4.04 ± 0.43	4.07 ± 0.46	4.05 ± 0.40	0.963

Table 2: Clinical outcomes at baseline, 1 month and 3 months

Parameter / Group	Baseline	1 month	3 months	Mean change	Within-group p-value
PI / Placebo	2.65 ± 0.24	1.54 ± 0.21	0.90 ± 0.15	1.75 ± 0.28	<0.001
PI / 1% Metformin	2.69 ± 0.16	1.52 ± 0.24	0.91 ± 0.18	1.78 ± 0.24	<0.001
PI / 1% Nano-metformin	2.63 ± 0.21	1.55 ± 0.18	0.90 ± 0.21	1.73 ± 0.30	<0.001
GI / Placebo	2.11 ± 0.20	1.50 ± 0.19	1.00 ± 0.23	1.11 ± 0.27	<0.001
GI / 1% Metformin	2.19 ± 0.17	1.10 ± 0.21	0.80 ± 0.24	1.39 ± 0.25	<0.001
GI / 1% Nano-metformin	2.33 ± 0.16	1.00 ± 0.18	0.60 ± 0.19	1.73 ± 0.22	<0.001
PPD / Placebo	7.15 ± 0.49	6.16 ± 0.40	5.35 ± 0.45	1.80 ± 0.52	<0.001
PPD / 1% Metformin	7.19 ± 0.52	5.67 ± 0.48	4.49 ± 0.42	2.70 ± 0.58	<0.001
PPD / 1% Nano-metformin	7.17 ± 0.47	5.17 ± 0.51	3.97 ± 0.33	3.20 ± 0.49	<0.001
CAL / Placebo	6.06 ± 0.47	5.40 ± 0.63	4.80 ± 0.65	1.26 ± 0.65	<0.001
CAL / 1% Metformin	6.09 ± 0.59	4.80 ± 0.62	3.90 ± 0.67	2.19 ± 0.72	<0.001
CAL / 1% Nano-metformin	6.08 ± 0.60	4.50 ± 0.80	3.30 ± 0.62	2.78 ± 0.68	<0.001

Table 3: Radiographic outcome and intergroup comparison of mean change scores

Outcome	Placebo	1% Metformin	1% Nano-metformin	F-value	p-value
IBD depth at baseline (mm)	4.04 ± 0.43	4.07 ± 0.46	4.05 ± 0.40	0.038	0.963
IBD depth at 6 months (mm)	3.20 ± 0.43	2.20 ± 0.34	1.70 ± 0.28	121.85	<0.001
ΔPI	1.75 ± 0.28	1.78 ± 0.24	1.73 ± 0.30	0.252	0.778
ΔGI	1.11 ± 0.27	1.39 ± 0.25	1.73 ± 0.22	45.67	<0.001
ΔPPD (mm)	1.80 ± 0.52	2.70 ± 0.58	3.20 ± 0.49	52.89	<0.001
ΔCAL (mm)	1.26 ± 0.65	2.19 ± 0.72	2.78 ± 0.68	38.45	<0.001
ΔIBD (mm)	0.84 ± 0.48	1.87 ± 0.45	2.35 ± 0.38	89.56	<0.001

Discussion:

The present split-mouth randomized clinical study showed that sub-gingivally delivered metformin gel improved periodontal healing when used as an adjunct to scaling and root planing and that the nano-metformin formulation produced the most favorable clinical and radiographic response. The three principal outcomes-probing pocket depth reduction, clinical attachment gain and intrabony defect depth reduction-showed a consistent graded pattern: placebo showed improvement, conventional metformin showed greater improvement and nano-metformin showed the greatest improvement. This pattern suggests that the observed benefit was not limited to plaque control alone but

reflected added biological activity from metformin and enhanced delivery through nano-formulation. The comparable plaque index changes across the three groups are clinically important because they indicate that oral hygiene improvement and professional debridement were similar for all sites. The absence of a significant difference in plaque reduction reduces the likelihood that superior outcomes in the metformin groups were simply caused by better plaque control. In contrast, gingival index reduction was significantly greater in metformin-treated sites, supporting an anti-inflammatory effect that aligns with the current understanding of periodontitis as a disease driven by dysregulated host-microbial interaction **[1, 2]**. The stronger gingival response in the nano-metformin group is also biologically plausible because local carriers can improve retention and drug availability inside the periodontal pocket **[9, 10]**. Scaling and root planing remains indispensable because mechanical disruption of biofilm is the foundation of periodontal therapy **[5]**. The placebo group in this study improved significantly in all clinical parameters, confirming the therapeutic value of conventional non-surgical treatment. However, residual deep sites after instrumentation remain a clinical challenge, particularly when access is limited by root anatomy or defect morphology **[6]**. The greater probing depth reduction in metformin groups supports the use of locally delivered adjuncts in selected sites where mechanical therapy alone may not provide optimal resolution. The clinical attachment level findings were especially relevant. At 3 months, the mean attachment gain was 1.26 mm in the placebo group, 2.19 mm in the 1% metformin group and 2.78 mm in the 1% nano-metformin group. These results are consistent with earlier clinical studies reporting attachment gain and pocket depth reduction after local metformin delivery **[11-14]**. They are also in agreement with evidence synthesis showing that metformin used with scaling and root planing can improve clinical and radiographic parameters in periodontal defects **[15]**. The magnitude of attachment gain in the nano-metformin group suggests that nano-formulation may improve the efficiency of drug delivery and prolong exposure at the diseased site. Radiographic intrabony defect reduction provided additional evidence of a regenerative effect. The mean defect fill was 0.84 mm in the placebo group, 1.87 mm in the 1% metformin group and 2.35 mm in the nano-metformin group. This is clinically meaningful because intrabony defects represent localized vertical bone loss and are more likely to benefit from regenerative or host-modulatory strategies. Experimental models have shown that metformin can reduce alveolar bone destruction and influence pathways related to osteoblast activity, osteoclast regulation, inflammation, oxidative stress and bone metabolism **[16, 17]**. These mechanisms may explain why metformin-treated sites showed greater bone fill than placebo-treated sites. The superiority of nano-metformin may be explained by its delivery characteristics. Nanoparticle-based periodontal systems can increase surface area, improve dispersion, enhance penetration into confined periodontal environments and support more controlled release of therapeutic agents **[18]**. In this study, nano-metformin produced the lowest final probing pocket depth, the greatest attachment gain and the greatest radiographic intrabony defect reduction. These findings suggest that the nano-formulation may have improved local bioavailability of metformin and sustained its anti-inflammatory and osteogenic effects within the periodontal defect. Despite these strengths, certain limitations should be considered. The study was single-center in design with a relatively small sample size and the follow-up period for clinical parameters was limited to 3 months. Radiographic assessment was performed with standardized intraoral periapical radiographs, which are practical and reproducible but do not provide three-dimensional defect analysis. The baseline gingival index differed significantly among groups and although the nano-metformin group showed the greatest improvement despite higher baseline inflammation, future studies should attempt stricter baseline balance. Microbiological, biochemical and patient-reported outcomes were not included, so the mechanism of healing could not be directly confirmed. Future research should include larger multicenter randomized trials, longer follow-up periods, three-dimensional radiographic evaluation and biologic markers such as inflammatory cytokines, bone turnover markers and gingival crevicular fluid mediators. Evaluation of release kinetics, sub-stantivity, safety and patient acceptance of nano-metformin formulations would also strengthen translational relevance. Within the limits of this study, however, nano-metformin appears to be a promising local adjunct that may improve both clinical healing and radiographic defect resolution in chronic periodontitis. A recent randomized double-blind trial using a 1% metformin biodegradable chip with SRP also reported significant CAL improvement and a greater reduction in *Porphyromonas gingivalis* load, supporting the local adjunctive role of metformin; however, its chip-based delivery and parallel-group design differ from the present gel-based split-mouth approach **[19]**.

Conclusion:

Scaling and root planing improved periodontal outcomes in all groups. Adjunctive 1% metformin produced greater clinical and radiographic benefits than placebo. Nano-metformin showed the best overall outcomes and appears promising for intrabony defects.

References:

[1] Papapanou PN *et al. J Periodontol*. 2018 **89**:S173. [PMID: 29926951]
[2] Kinane DF *et al. Nat Rev Dis Primers*. 2017 **3**:17038. [PMID: 28805207]
[3] Trindade D *et al. J Clin Periodontol*. 2023 **50**:604. [PMID: 36631982]
[4] Hajishengallis G. *Nat Rev Immunol*. 2015 **15**:30. [PMID: 25534621]
[5] Sanz M *et al. J Clin Periodontol*. 2020 **47**:4.[PMID: 32383274]
[6] Cobb CM & Sottosanti JS. *J Periodontol*. 2021 **92**:1370. [PMID: 33660307]
[7] Smiley CJ *et al. J Am Dent Assoc*. 2015 **146**:508. [PMID: 26113099]

[8] Herrera D *et al. J Clin Periodontol*. 2002**29**:136.[PMID: 12787214]
[9] Sholapurkar A *et al. Dent J (Basel)*. 2020 **9**:2. [PMID: 33375176]
[10] de Sousa TL *et al. Front Bioeng Biotechnol*. 2024 **12**:1427758. [PMID: 39081330]
[11] Pradeep AR *et al. J Periodontol*. 2013 **84**:212. [PMID: 22509750]
[12] Rao NS *et al. J Periodontol*. 2013 **84**:1165. [PMID: 23130655]
[13] Pradeep AR *et al. J Investig Clin Dent*. 2016 **7**:239. [PMID: 25787121]
[14] Pradeep AR *et al. J Periodontol*. 2017 **88**:1023. [PMID: 28731373]
[15] Akram Z *et al. J Periodontal Res*. 2018 **53**:941. [PMID: 29858876]
[16] Bak EJ *et al. J Periodontol*. 2010 **81**:412. [PMID: 20192868]
[17] de Araujo AA *et al. PLoS One*. 2017 **12**:e0183506. [PMID: 28847008]
[18] Basudan AM. *Saudi Dent J*. 2022 **34**:669. [PMID: 36570572]
[19] Soundarya D *et al. Cureus*. 2025 **17**:e84248. [PMID: 40530190]