Original Article

CLINICAL AND RADIOGRAPHIC EVALUATION OF METFORMIN-LOADED COLLAGEN MEMBRANE IN RECONSTRUCTIVE PERI-IMPLANT DISEASE SURGERY: A ONE-YEAR STUDY

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ABSTRACT

Peri-implantitis is a destructive inflammatory disease that compromises implant survival, oral health, and patient well-being. Metformin, a widely used medicine, possesses anti-inflammatory and osteogenic properties that may enhance regenerative outcomes in peri-implant therapy. To evaluate the clinical and radiographic outcomes of a metformin-loaded collagen membrane as an adjunct to reconstructive surgical therapy for peri-implantitis. Fifty-two systemically healthy participants with peri-implantitis-associated infrabony defects were enrolled in this prospective one-year clinical study. Group A (n=26) received xenogeneic bone grafting with a conventional collagen membrane, while Group B (n=26) received xenogeneic bone grafting with a metformin-loaded collagen membrane. Clinical parameters (PI, GI, PPD, and CAL) and radiographic bone level (BL) were assessed at baseline and one year. Both groups demonstrated significant improvements in all clinical and radiographic parameters after one year ($p < 0.001$). However, Group B showed significantly greater reductions in PI, GI, PPD, CAL, and BL compared with Group A ($p < 0.001$), indicating enhanced inflammation control and peri-implant tissue regeneration. The adjunctive use of a metformin-loaded collagen membrane resulted in superior clinical and radiographic outcomes compared with a conventional collagen membrane. Local metformin delivery may represent a promising regenerative strategy for peri-implantitis management, thereby supporting oral health and patient wellbeing.

Key words: Disease, Guided bone regeneration, Peri-implant disease, Regeneration, Wellbeing.

Introduction

Dental implants are a predictable and widely accepted treatment option for replacing missing teeth, providing favorable long-term functional and esthetic outcomes [1]. The success of implant therapy depends on the establishment and maintenance of osseointegration, which may be influenced by implant characteristics, surgical and prosthetic factors, systemic conditions, and patient-related behaviors [2, 3]. Despite high survival rates, biological complications remain a major challenge affecting long-term implant success.

Peri-implant diseases comprise peri-implant mucositis, a reversible inflammatory condition confined to the peri-implant soft tissues, and peri-implantitis, a destructive inflammatory disease characterized by progressive loss of supporting bone. The pathogenesis of peri-implantitis involves a complex interaction between microbial biofilms and the host immune-inflammatory response. Biofilm accumulation on implant surfaces triggers the release of inflammatory mediators and osteoclast-activating factors, resulting in connective tissue breakdown and progressive bone destruction [4]. Several risk factors, including poor plaque control, previous periodontal disease, smoking, diabetes, inadequate maintenance, residual cement, and biomechanical overload, have been associated with disease development and progression [5-7].

Management of peri-implantitis remains challenging because treatment must simultaneously control infection, reduce inflammation, detoxify implant surfaces, and regenerate lost supporting tissues. While non-surgical therapy may be effective in reducing soft tissue inflammation, its benefits are often limited in advanced lesions with intrabony defects [8]. Consequently, reconstructive surgical therapy has become an important treatment modality for peri-implantitis, particularly in defects amenable to regenerative procedures. Such approaches typically involve implant surface decontamination followed by placement of bone graft materials and barrier membranes to facilitate guided bone regeneration [9].

Recent advances in peri-implant therapy have focused on enhancing regenerative outcomes through biologically active implant coatings and local drug-delivery systems [10-14]. Although implant surface modifications may improve

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resistance to microbial colonization, their clinical application is primarily preventive in nature. In contrast, incorporation of therapeutic agents into regenerative biomaterials such as grafts and membranes offers a practical strategy for delivering bioactive molecules directly to diseased peri-implant sites during surgical treatment [15].

Metformin, a commonly used antihyperglycemic drug, has attracted considerable interest in regenerative dentistry because of its anti-inflammatory, antioxidant, and osteogenic properties [16]. Experimental studies have demonstrated that metformin can inhibit osteoclastic activity, modulate inflammatory responses, and promote osteoblastic differentiation and bone formation [17, 18]. These biological effects suggest that local delivery of metformin may enhance both resolution of inflammation and regeneration of peri-implant hard tissues. Collagen membranes, owing to their biocompatibility and widespread use in guided bone regeneration, represent a suitable carrier for localized drug delivery while simultaneously functioning as a regenerative barrier membrane [19].

Despite increasing evidence supporting the regenerative potential of metformin, limited clinical data are available regarding the use of metformin-loaded collagen membranes in reconstructive peri-implantitis therapy. Therefore, the prospective one-year clinical study was undertaken to evaluate the clinical and radiographic outcomes of a metformin-loaded collagen membrane used in conjunction with xenogeneic bone grafting during reconstructive surgical management of peri-implant disease.

Materials and Methods

Study design and participant selection

This prospective clinical study was carried out in the Department of Periodontics, Saveetha Dental College and Hospitals, Chennai, from February 2025 to April 2026. Ethical clearance was granted by the Institutional Ethics Committee of Saveetha Dental College and Hospitals (SRB/SDC/MSIMPLANT-2409/25/250). The study was performed in accordance with the ethical standards of the Declaration of Helsinki (2013). Before participation, all individuals provided written informed consent.

Fifty-two systemically healthy participants between 30 and 55 years of age were enrolled. Each participant presented with a single implant diagnosed with peri-implantitis and associated with an infrabony defect requiring reconstructive surgical management. The required sample size was determined using G*Power software (Version 3.1.9.4), utilizing the mean and standard deviation values reported in a previous investigation [20]. Calculations were performed with a confidence level of 95% and a statistical power of 80%, yielding a total sample size requirement of 52 subjects.

Peri-implantitis was diagnosed according to the consensus recommendations of the 8th European Workshop on Periodontology [21]. Individuals were considered eligible when peri-implant probing depth (PPD) was ≥5 mm in conjunction with bleeding on probing (BOP) and/or suppuration and an infrabony defect depth of at least 3 mm. Exclusion criteria comprised systemic disorders or medical conditions capable of affecting wound healing, contraindications to surgical treatment, antibiotic therapy within the previous three months, implant placement or prosthetic loading within the preceding year, implant mobility, signs of occlusal overload, and prosthetic restorations that could not be removed.

Participants were allocated into two treatment groups. Group A (n = 26) underwent reconstructive peri-implant surgery using a xenogeneic bone graft in combination with a conventional collagen membrane. Group B (n = 26) received the same reconstructive procedure using a xenogeneic bone graft covered with a metformin-loaded collagen membrane.

Surgical procedure and postoperative care

Before surgical intervention, all participants received initial periodontal therapy consisting of oral hygiene instruction along with supra- and subgingival mechanical debridement of both teeth and implants. This phase was completed four weeks prior to surgery to achieve adequate control of inflammation. Surgical treatment was initiated only after completion of all required periodontal therapy.

Immediately before surgery, implant-supported prosthetic restorations were removed and replaced with cover screws. Following healing, the prosthetic components were reinstalled. All surgical procedures were performed by a single experienced operator (KK).

After administration of local anesthesia, sulcular incisions were made around the affected implant and extended to the adjacent sites. Full-thickness mucoperiosteal flaps were then elevated on the buccal and lingual/palatal aspects to provide access to the defect. Granulation tissue was thoroughly debrided, and the implant surface was mechanically detoxified using titanium curettes (Hu-Friedy®, Chicago, USA), followed by abundant irrigation with sterile saline solution.

Defects in both groups were filled with a xenogeneic particulate bone substitute (Bio-Oss®). In Group A, the grafted site was covered with a conventional bioresorbable collagen membrane (Creos®). In Group B, the grafted site was covered with a metformin-loaded bioresorbable collagen membrane (Creos®). For preparation of the metformin membrane, 10 mg of metformin hydrochloride was blended with 0.2 mL of sterile distilled water to form a homogeneous paste. The paste was uniformly spread over the surface of the membrane facing the defect immediately before placement. Following membrane adaptation, the flaps were repositioned and sutured using 4-0 non-absorbable black silk sutures.

Postoperative medication consisted of amoxicillin 500 mg administered three times daily for three days and Zerodol-SP twice daily for three days. Participants were instructed to rinse with 0.12% chlorhexidine mouthwash twice daily and to avoid brushing or interdental cleaning in the treated region for two weeks. Suture removal was performed at the two-week postoperative visit.

After surgery, all participants were included in a supportive peri-implant maintenance program and were reviewed every three months for one year. Reinforcement of oral hygiene measures was provided at each recall appointment, and mechanical debridement was performed whenever indicated to ensure effective plaque control and reduce its potential influence on treatment outcomes.

Clinical and radiographic evaluation

Clinical measurements were recorded by a calibrated examiner (AR). The evaluated parameters included plaque index (PI) according to Silness and Löe, gingival index (GI) according to Löe and Silness, peri-implant probing depth (PPD), and clinical attachment level (CAL). PPD and CAL measurements were obtained at six sites around each implant using a standardized periodontal probe (Hu-Friedy®, Chicago, USA). To ensure consistency, all recordings were made by the same examiner throughout the study period.

Standardized intraoral periapical radiographs were acquired at baseline and after one year using the long-cone paralleling technique. Measurements obtained from the mesial and distal surfaces of each implant were averaged before statistical analysis. Radiographic assessment included evaluation of bone level (BL), defined as the linear distance from the implant shoulder to the most apical extent of the osseous defect. Clinical and radiographic assessments were performed at baseline and repeated at the one-year follow-up.

Statistical analysis

The data were processed using the Statistical Package for the Social Sciences (SPSS Software, Version 23.0; IBM Corp., Armonk, NY, USA). The Shapiro-Wilk and Kolmogorov-Smirnov tests confirmed a normal distribution. Comparisons of age, PI, GI, PPD, CAL, and BL between the two groups were performed using an independent t-test. Gender distribution was evaluated with the Chi-square test. Intragroup comparisons were carried out using a paired t-test. A p-value of less than 0.05 was considered to be statistically significant.

Results and Discussion

Group 1 comprised 13 males and 13 females, with a mean age of 48.5 ± 4.92 years, whereas Group 2 included 14 males and 12 females, with a mean age of 49.6 ± 3.87 years. Comparison of baseline demographic characteristics revealed no statistically significant differences between the groups with respect to age or sex distribution ($p > 0.05$).

Table 1 presents the intergroup comparison of clinical and radiographic parameters between Group A and Group B at baseline and after one year. At baseline, no statistically significant differences were observed between the groups for PI, GI, PPD, CAL, and BL ($p > 0.05$), indicating comparable baseline characteristics. At the one-year follow-up, both groups demonstrated improvement in all evaluated parameters. However, Group B showed significantly lower PI, GI, PPD, CAL, and BL values than Group A ($p < 0.001$), indicating superior clinical and radiographic outcomes following treatment with the metformin-loaded collagen membrane.

Table 1. Intergroup comparison between both groups at baseline and 1 year

Variable	Baseline Group A (Control)	Baseline Group B (Test)	p-value (Baseline)	1 year Group A (Control)	1 year Group B (Test)	p value (1 year)
Plaque Index (PI)	2.63 ± 0.17	2.67 ± 0.13	0.35	1.42 ± 0.05	0.51 ± 0.04	<0.001*
Gingival Index (GI)	2.49 ± 0.19	2.52 ± 0.17	0.55	1.21 ± 0.07	0.49 ± 0.06	<0.001*
Peri-implant Pocket Depth (PPD)	5.92 ± 1.22	5.99 ± 1.20	0.84	3.40 ± 0.11	2.39 ± 0.10	<0.001*
Clinical Attachment Level (CAL)	5.98 ± 1.27	6.03 ± 1.21	0.89	3.44 ± 0.15	2.41 ± 0.11	<0.001*
Bone Level (BL)	6.72 ± 1.41	6.89 ± 1.49	0.67	4.32 ± 0.21	3.16 ± 0.12	<0.001*

*Statistically significant

Table 2 depicts the intragroup comparison of clinical and radiographic parameters from baseline to one year within each study group. Both Group A and Group B exhibited statistically significant reductions in PI, GI, PPD, CAL, and BL at the one-year follow-up compared with baseline values ($p < 0.001$). Although significant improvements were observed in both groups, the magnitude of improvement was greater in Group B, suggesting that the adjunctive use of a metformin-loaded collagen membrane enhanced the clinical and radiographic benefits of reconstructive surgical therapy for peri-implant disease.

Table 2. Intragroup comparison of both groups from baseline to 1 year

Variable	Baseline Group A (Control)	1 year Group A (Control)	p-value (Group A)	Baseline Group B (Test)	1 year Group B (Test)	p-value (Group B)
Plaque Index (PI)	2.63 ± 0.17	1.42 ± 0.05	<0.001*	2.67 ± 0.13	0.51 ± 0.04	<0.001*
Gingival Index (GI)	2.49 ± 0.19	1.21 ± 0.07	<0.001*	2.52 ± 0.17	0.49 ± 0.06	<0.001*
Peri-implant Pocket Depth (PPD)	5.92 ± 1.22	3.40 ± 0.11	<0.001*	5.99 ± 1.20	2.39 ± 0.10	<0.001*
Clinical Attachment L (CAL)	5.98 ± 1.27	3.44 ± 0.15	<0.001*	6.03 ± 1.21	2.41 ± 0.11	<0.001*
Bone Level (BL)	6.72 ± 1.41	4.32 ± 0.21	<0.001*	6.89 ± 1.49	3.16 ± 0.12	<0.001*

*Statistically significant

Peri-implant disease remains a significant biological complication associated with dental implants and is characterized by progressive inflammation and loss of supporting peri-implant tissues. Although reconstructive surgical therapy combined with bone grafting has demonstrated favorable outcomes, achieving predictable regeneration of lost peri-implant tissues remains challenging. Metformin, a widely used antihyperglycemic agent, has recently attracted considerable attention in periodontal and implant research because of its anti-inflammatory, antioxidant, osteogenic, and bone regenerative properties. Therefore, the present prospective one-year clinical study was designed to evaluate the effectiveness of a metformin-loaded collagen membrane used in conjunction with xenogeneic bone grafting during reconstructive surgical management of peri-implant disease.

The findings of the present study demonstrated that both treatment groups showed significant improvements in clinical and radiographic parameters after one year when compared with baseline values. However, the group treated with the metformin-loaded collagen membrane exhibited significantly greater reductions in PI, GI, PPD, CAL, and radiographic bone loss than the control group. These findings suggest that local delivery of metformin through a collagen membrane may provide additional therapeutic benefits beyond those achieved with reconstructive surgery and xenogeneic bone grafting alone.

The significant reduction in plaque and gingival indices observed in the metformin group may be attributed to the anti-inflammatory properties of metformin. Experimental and clinical evidence has demonstrated that metformin can modulate inflammatory pathways, suppress pro-inflammatory cytokine production, and reduce oxidative stress, thereby contributing to improved peri-implant tissue health. Aljofi *et al*. [22] reported that metformin positively influences periodontal and peri-implant soft- and hard-tissue healing by reducing inflammation, oxidative stress, and subsequent bone loss. Their review highlighted consistent improvements in both clinical and radiographic outcomes across animal and human studies, supporting the favorable tissue response observed in the present investigation.

The greater reductions in probing pocket depth and clinical attachment loss noted in the test group are also consistent with previous reports evaluating locally delivered metformin in periodontal and peri-implant therapy. Kamalakannan *et al*. [23] demonstrated that adjunctive application of 1% metformin gel following mechanical debridement in peri-implantitis patients resulted in significantly lower PI, GI, PPD, CAL, and peri-implant crevicular fluid IL-6 levels compared with debridement alone. Although the therapeutic approach in their study differed from the present investigation, both studies suggest that local metformin delivery enhances peri-implant tissue healing and improves clinical outcomes. The superior reduction in inflammatory parameters observed in their study may explain the enhanced pocket resolution and attachment gain identified in the current trial.

The favorable radiographic outcomes observed in the metformin-treated group may be related to the osteogenic and regenerative potential of metformin. Increasing evidence suggests that metformin stimulates osteoblast differentiation, promotes mineralization, enhances expression of osteogenic markers, and supports new bone formation. Lin *et al*. [24] demonstrated that local metformin administration around dental implants increased osteogenic differentiation, improved bone microarchitecture, and accelerated osseointegration in osteoporotic models. Their findings provide a biological basis for the enhanced radiographic bone fill and reduced peri-implant bone loss observed in the present study.

Similarly, Patel *et al*. [25], in their systematic review, concluded that metformin may improve osseointegration and peri-implant bone preservation through its ability to stimulate osteoblastic activity and bone formation. Although most available evidence originates from preclinical studies, the enhanced radiographic outcomes observed in the present clinical trial appear to support these proposed mechanisms. The findings further suggest that local delivery systems capable of maintaining sustained metformin release at the surgical site may create a microenvironment favorable for peri-implant bone regeneration.

The use of a collagen membrane as a carrier for metformin may have further contributed to the observed outcomes. Collagen membranes are widely used in regenerative procedures because of their excellent biocompatibility, space-maintaining ability, and capacity to serve as vehicles for bioactive agents [26]. In the present study, the membrane likely facilitated localized and sustained release of metformin directly within the regenerative site, thereby maximizing its biological activity while minimizing systemic exposure. The synergistic combination of xenogeneic bone grafting, guided tissue regeneration principles, and local metformin delivery may therefore explain the superior clinical and radiographic improvements achieved in the test group.

Although studies evaluating metformin-loaded collagen membranes in peri-implant reconstructive surgery are currently unavailable, indirect evidence from periodontal regeneration research supports the present findings. Najeeb *et al*. [27] reported that topical metformin application significantly improved clinical and radiographic outcomes in periodontal intrabony defects. Likewise, Nicolini *et al*. [28] demonstrated through systematic review and meta-analysis that adjunctive metformin provided additional reductions in probing depth and gains in clinical attachment level when combined with conventional periodontal therapy. While these investigations were conducted in periodontal defects rather than peri-implant lesions, both conditions share common inflammatory and bone-destructive pathways. Therefore, the regenerative benefits observed in periodontal therapy may partially explain the positive outcomes achieved in the current peri-implant setting.

Recent evidence has further emphasized the potential role of metformin as a bioactive adjunct in regenerative implant therapy. Hu *et al*. [29] developed a metformin-containing multifunctional hydrogel for peri-implantitis treatment and demonstrated significant reductions in inflammatory mediators and peri-implant bone loss in experimental models. Although the delivery platform and study design differed substantially from the present investigation, both studies support the concept that local metformin administration can simultaneously modulate inflammation and enhance bone repair around implants. These findings collectively reinforce the growing interest in repurposing metformin as a regenerative biomolecule in implant dentistry.

The present findings should be interpreted in light of the broader evidence summarized by recent systematic reviews. Uddin *et al*. [30] reported that local metformin delivery consistently improved bone regeneration, clinical attachment gain, and probing depth reduction across a wide range of periodontal studies. However, they also highlighted substantial heterogeneity among investigations, short follow-up periods, and the need for well-designed long-term clinical trials. The current study contributes to addressing this gap by providing one-year clinical and radiographic data in peri-implant disease management, an area where evidence remains limited.

A notable strength of the present study is its prospective design, one-year follow-up period, and comprehensive assessment of both clinical and radiographic outcomes. Furthermore, to the best of our knowledge, this is among the first clinical investigations evaluating a metformin-loaded collagen membrane as an adjunct to reconstructive peri-implant surgery using xenogeneic bone grafting. The findings provide preliminary clinical evidence supporting the regenerative potential of this novel therapeutic approach.

Overall, the results of the present study suggest that incorporation of metformin into a collagen membrane may represent a promising and biologically driven adjunctive approach for reconstructive peri-implant therapy. By combining anti-inflammatory and osteogenic properties with a localized drug delivery platform, metformin-loaded collagen membranes have the potential to enhance peri-implant tissue regeneration and improve long-term treatment outcomes. Further well-designed clinical trials are warranted to validate these findings and facilitate their translation into routine clinical practice.

Limitations

The sample size was relatively modest, and evaluation was limited to clinical and radiographic parameters without assessment of microbiological, immunological, or histological outcomes. In addition, the study evaluated a single concentration of metformin and a single membrane formulation. Future studies with larger multicenter populations, longer follow-up durations, advanced three-dimensional radiographic analysis, and biomarker-based assessments are required to further elucidate the mechanisms underlying the observed benefits. Comparative investigations evaluating different metformin concentrations, delivery systems, and regenerative protocols may also help establish optimized treatment strategies.

Conclusion

Within the limitations of this prospective one-year clinical study, the use of a metformin-loaded collagen membrane in conjunction with xenogeneic bone grafting resulted in significantly superior clinical and radiographic outcomes compared with a conventional collagen membrane. The findings suggest that local metformin delivery may enhance peri-implant tissue healing and bone regeneration, making it a promising adjunctive regenerative approach for peri-implant disease management. Further long-term randomized clinical trials with larger sample sizes are warranted to validate these findings.

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Conflict of interest: None

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Ethics statement: The study protocol was approved by the Institutional Ethics Committee of Saveetha Dental College and Hospitals, Chennai, India.

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