



## Metformin Gel as Locally Delivered Adjunctive Therapy for Periodontitis Stage II, Grade B (A Randomized Controlled Clinical Trial with Quantitative Bacterial Assessment)

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### Abstract

**Background:** Periodontal disease is one of the most common oral diseases that affects the general public, although a number of surgical and pharmacological options are available for the management of periodontitis yet it still affects a large proportion of population. Metformin is a second-generation biguanide anti-diabetic agent used to treat type II diabetes, Metformin has been used along with surgical and non-surgical periodontal therapy, as treatment for periodontitis. It has been reported to relieve clinical symptoms as BOP, PD and CAL. This study was carried out to investigate the clinical and microbiological effectiveness of 1% Metformin gel on Stage II grade B periodontitis. The rationale behind using Metformin is that it has a potential antimicrobial effect, also, It inhibits osteoclast formation and activity in periodontitis patients at the cellular level as well.

**Method:** a 37 year old female patient diagnosed with stage II grade B periodontitis, was treated with SRP combined with intrasulcular application of 1% Metformin gel at the deepest pocket of 5 mm PD and 4mm CAL and follow up period 6 months. GCF sample was collected at baseline and 2 weeks and RT-PCR was done to detect A.A and P.gingivalis at different time intervals.

**Results.** 1% Metformin gel improves the periodontal health with statistically significant improvement in the PPD, CAL, PI and GI values along with a significant decrease in all types of bacteria (A.A., P.gingivalis).

**Conclusion:** the use of 1% metformin gel as adjunct to non-surgical periodontal therapy (NSPT) provided a significant improvement in the clinical periodontal parameters in stage II grade B periodontitis and showed a statistically significant reduction in the bacteria load of (P.gingivalis, T.pallidum, A.A. and P. intermedia) from baseline to 2 weeks and 2 months.

**Keywords:** Metformin; Periodontitis; Bacterial; PPD

### Introduction

Periodontitis is defined as a multifactorial chronic inflammatory disease that is associated with dysbiotic plaque biofilms and also characterized by progressive destruction of the tooth-supporting apparatus manifested as loss of clinical attachment, presence of periodontal pockets, persistent gingival bleeding and manifested radiographically as alveolar bone loss [1].

Periodontal therapy is always started by periodontal pocket debridement (PPD) which is considered the gold standard of non-

surgical periodontal therapy (NSPT). PPD procedures consist of mechanical supra and subgingival pocket debridement. It has been postulated according to, that a single session of scaling and root planning can disrupt the proportions of specific bacterial forms in the subgingival periodontal flora. Moreover, debridement decreased probing depth considerably [2].

Metformin is a second-generation biguanide anti-diabetic agent used to treat type II diabetes. It lowers blood glucose by reducing hepatic glucose production, a process known as gluconeogenesis

inhibition and insulin resistance. It is currently recommended as first-line therapy in obese patients suffering from this condition [3].

An early experimental research has demonstrated the effect of systemic metformin administration on alveolar bone resorption. The periapical bone loss area was significantly reduced in the metformin-treated group. Metformin inhibited periapical lesions by reducing the number of osteoclasts and bone resorption areas in rat model [4].

Studies investigated the effect 1% Metformin gel used as an adjunct to SRP. Clinical parameters such as plaque index, modified sulcus bleeding index, probing depth and clinical attachment level were assessed at baseline, at 3-, and at 6-months periods. The studies confirmed that 1% Metformin has significantly improved clinical and radiographic parameters in intrabony defects in patients with chronic periodontitis.

The gap of knowledge was to investigate the quantitative changes of two major periodontal pathogens (*A. actinomycetemcomitans* (A.A.), *P. gingivalis* (Pg), in GCF samples using real-time PCR assays in patients with stage II, grade B periodontitis along with assessing the periodontal clinical parameters after SRP with or without using 1% Metformin gel locally delivered.

### Case Description

A 37 years old female patient presented to Ain shams, Periodontology department with a chief complain of bleeding gums and inability to chew food, the patient was medically free. Upon clinical diagnosis the patient was diagnosed as a stage II grade B periodontitis patient. Initial examination was done including full mouth probing using UNC15<sup>1</sup> Periodontal probe followed by periapical radiographic examination for the selected sites (PPD ≤ 5mm). Patient motivation and education for proper oral hygiene instructions included twice-daily tooth brushing with soft toothbrush using modified bass brushing technique and once daily interdental cleaning with dental floss and interdental brushes for wide interproximal embrasure spaces. Full mouth supra and subgingival debridement was performed using ultrasonic device with supragingival scaling tips followed by universal and Gracey's curettes<sup>2</sup> for proper subgingival debridement. Local anesthesia was used for patient's comfort whenever needed. After 48 hours from the last periodontal instrumentation visit, patient was recalled for recording baseline clinical parameters and collecting the baseline GCF sample, then local drug application.

GCF sample was collected using Perio paper strip<sup>3</sup> was inserted into the sulcus until resistance is felt for 30 seconds and then removed, after collection of gingival fluid the strips were placed in a sterile plastic tube. GCF samples were stored at -20 C until further analysis after collecting all the samples in 2 weeks duration. After collecting GCF samples, application of the intervention takes place, A sterile 1ml micro-syringe was filled with the medication and then it was injected into the sulcus, filling the whole interdental area.

All clinical periodontal parameters were assessed at baseline, after 3 months and 6 months.

### Results

There was a statistical significant results in all parameters 6 months, CAL showed a statistical significance difference at 6 months' time interval, PI showed insignificant results at 6 months follow in comparison to baseline, for GI lower values were detected at 6 months, moreover the PPD shower a decrease in pocket depth 6 months interval.



Figure 1



Figure 2

<sup>1</sup>UNC15 Periodontal probe, Nordent Manufacturing Inc, USA

<sup>2</sup>HuFriedy universal and Gracey's curette; HuFriedy, Chicago, USA.



Figure 3



Figure 4

Time	Mean	SD
baseline	0.625	0.518
6 months	0.375	0.518

Table a: Plaque index.

Time	Mean	SD
Baseline	1.50	0.52
6 months	0.38	0.53

Table b: Gingival index.

Time	Mean	SD
Baseline	3.63	0.62
6 months	1.50	0.53

Table c: Clinical attachment level

Time	Mean	SD
baseline	4.50	0.53
6 months	2.13	0.35

Table d: Periodontal pocket depth.

Time	Microbial analysis			
	A. A.		P. gingival is	
	M	SD	M	SD
Baseline	9.72	4.74	5.83	1.61
2 weeks	4.72 a	2.3	2.86	0.64

Table e

### Discussion

Metformin gel was prepared to be sustained release gel (over 14 days) by using Poly lactic-co-Glycolic Acid (PLGA), it is a biocompatible and biodegradable synthetic polymer that has been approved by the United States Food and Drug Administration (USFDA). This preparation method was reported to prolong its release [5].

The patient included in our study was medically free in order to minimize the variables and to avoid any systemic disorders and certain medications that may affect the periodontal attachment apparatus and cause loss of periodontal attachment and alveolar bone.

The follow-up visits for re-evaluation of clinical and microbiological parameters were scheduled at 6 months along with 2 weeks interval from the baseline visit respectively (Greenstein, 2000). Meanwhile, similarly to previous studies Paradeep., *et al.* (2017); Kuldeep., *et al.* 2022, [6] reported that a period of 4-6 weeks may be sufficient to evaluate the effectiveness of non-surgical periodontal therapy (NSPT) in periodontal tissues and that post-treatment recovery occurs in 3-6 months in patients with good mechanical plaque control.

The PI was evaluated to monitor patients, compliance, since this parameter is mostly relied on patients. Moreover, the gingival index reflected the inflammatory status of the gingiva, while CAL and probing depth were the primary outcomes to assess the effect of the treatment of periodontal and alveolar bone tissues.

PCR method was used for quantitative microbiological analysis of GCF samples to identify Pg, A.A. as it is a rapid, sensitive, and reliable technique for the detection and quantification of individual microbial species. In addition, no significant difference in bacterial load value was detected in other studies after 3 months follow up.

PI significantly decreased using 1% Metformin. Pradeep., *et al.* Pankaj *et al.* have found similar results in their study using 1% MF gel where the PI was reduced from baseline to 6 months in the MF group as compared to the placebo group. Significant reduction in GI was found after using 1% MF, These results were in accordance

with the results were obtained by Pradeep., *et al.* Pankaj., *et al.* who found significant reduction in the modified SBI (mSBI) using 1% MF gel from baseline to 6 months. This could be attributed to the anti-inflammatory effect of metformin, the decrease of the bacterial load inside the pocket and to the patients cooperation and motivation during the follow up period following all the instructions also due to the process of soft tissue healing that occurs post non-surgical periodontal therapy.

In the present study, results showed a statistically significant reduction in pocket probing depth (PPD) at 6 months compared to baseline, Similar results were found in the study by Pradeep., *et al.* where mean PPD was reduced from  $8.16 \pm 0.75$  mm to  $5.36 \pm 0.77$  mm at 3 months and further reduced to  $4.36 \pm 0.81$  mm at 6 months after using 1.5% MF gel. Considering Clinical attachment level (CAL) gain as a clinical outcome, results of the present study showed a statistically significant CAL gain at 6 months postoperatively compared to baseline, This was in agreement with the study done by Pradeep., *et al.* where the mean CAL was reduced from  $6.30 \pm 0.79$  mm to  $3.93 \pm 0.74$  mm at 3 months and further reduced to  $2.70 \pm 0.75$  mm at 6 months when 1.5% MF gel was placed in Intra bony defects (IBD).

## Conclusion

1% metformin gel showed a statistically significant difference and decrease in bacterial load of the 2 different periodontal pathogens A. A., P. gingival is.

## Conflict of Interest

All authors have participated in conception, design, drafting the article and approval of the final version. The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript.

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