Evaluation of the Use of Locally Delivered Metformin as An Adjunctive Therapy to Non-Surgical Periodontal Treatment

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ABSTRACT

Background: Periodontitis is an ongoing inflammatory reaction to oral biofilm. Clinical signs of the disease include loss of connective tissue attachment and bone around the teeth, as well as the formation of periodontal pockets due to apical migration of the junctional epithelium. MMP and cytokines are examples of inflammatory mediators that are produced as part of the host response and contribute to tissue destruction. To avoid periodontal surgeries for deep pockets, several local drug delivery (LDD) systems have been developed to avoid the negative effects of systemic antibiotic administration. Metformin (MF) is a biguanide and one of the most commonly used oral hypoglycemic drugs in type 2 diabetes. MF reduces plasma glucose by inhibiting glucose production by hepatic cells in the liver. Aside from lowering blood glucose levels, MF may have additional benefits such as weight loss, lower plasma lipid levels, and the prevention of some vascular complications.

Method: a 45 old male patient diagnosed with stage III periodontitis, was treated with SRP combined with intrasulcular application of 1% Metformin gel at the deepest pocket of 6 mm PD and 5 mm CAL and follow up period 6 months.

Results: 1% Metformin gel improved the periodontal health with statistically significant improvement in the PPD, CAL, PI and GI values.

Conclusion: The use of 1% metformin gel as adjunct to nonsurgical periodontal therapy (NSPT) provided a significant improvement in the clinical periodontal parameters.

Keywords: [Periodontitis; Metformin; Clinical Attachement Loss; Stage III Grade A]

1. 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. [6]

Pro-inflammatory and anti-inflammatory cytokines are part of the cytokine network that mediates the immune response. Numerous proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, are released from junctional epithelia, connective tissue fibroblasts, and macrophages during the initiation of an inflammatory response in the periodontal connective tissue. Gingival crevicular fluid from patients with chronic periodontitis or aggressive periodontitis is compared to that from gingivitis or healthy patients, the RANKL/OPG ratio is higher. [2]

Mechanical debridement is the first step in the treatment of periodontitis, which disturbs the biofilm and reduces the bacterial load. In some cases, the base of deep pockets of periodontitis is difficult to access with

periodontal instrumentation, making mechanical methods insufficient. To avoid periodontal surgeries for deep pockets, it is recommended that systemic or local chemotherapeutic agents be administered. Several local drug delivery (LDD) systems have been developed to avoid the negative effects of systemic antibiotic administration. Chlorhexidine, Tetracycline, and Metronidazole are examples of LDD that are used as an adjunctive aid in the treatment of periodontal diseases. [2]

Metformin (MF) is a biguanide and one of the most commonly used oral hypoglycemic drugs in type 2 diabetes. MF reduces plasma glucose by inhibiting glucose production by hepatic cells in the liver. Aside from lowering blood glucose levels, MF may have additional benefits such as weight loss, lower plasma lipid levels, and the prevention of some vascular complications. [3]

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]

So, the current study was conducted to evaluate the effect of using Metformin as an adjunct to non-surgical treatment of periodontitis.

2. Material and methods

2.1 Case Presentation

A 45-year-old male patient presented to Ain Shams, Periodontology department with a chief complaint of bleeding gums and inability to chew food, the patient was medically free. Upon clinical diagnosis the patient was diagnosed as a stage III Periodontitis.

Initial examination was done including full mouth probing using University of Michigan O' probe with Williams' graduations followed by periapical radiographic examination for the selected sites (PPD ≤ 6 mm).

2.2 Periodontal Treatment

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 curettes (2R-2L and 4R-4L) 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, then local drug application.

2.3 Clinical Evaluation

All clinical periodontal parameters (Plaque Index (PI), Gingival Index (GI), Pocket Depth (PD) and Clinical Attachment Level (CAL)) were assessed at baseline and 6 months and can be clearly seen in **Figures (1) and (2)**.

Results

There was a statistically significant results in all parameters at 6 months, PI, GI, PD and CAL were significantly lower as compared to baseline and can be clearly seen in **Tables (1), (2), (3) and (4)**.

Discussion

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 healing of the socket.

Metformin HCl (MF) is a second-generation biguanide, derived from French lilac (Galega officinalis), used to manage type 2 diabetes mellitus can reduce blood sugar by blocking the liver's gluconeogenesis (glucose production). The effects of MF on bone formation have also been shown to be positive. Increased proliferation of osteoblasts and decreased osteoclast activity have both been proposed as mechanisms of action for the osteogenic effect of MF. The proliferation of osteoblasts is found to increase after they take in MF, according to studies. [1]

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

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. [5] 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 patient's 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 periodontal pocket 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 ± 0.75 mm to 5.36 ± 0.77 mm at 3 months and further reduced to 4.36 ± 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 ± 0.79 mm to 3.93 ± 0.74 mm at 3 months and further reduced to 2.70 ± 0.75 mm at 6 months when 1.5% MF gel was placed in Intra bony defects (IBD).

Conclusion

The results of the present study show that local delivery of MF gel into periodontal pockets stimulated a significant increase in the PD reduction and CAL gain in adjunct to SRP. The 1% MF gel along with SRP was found to provide maximum improvement in clinical parameters. Thus bone-formative effects of the common oral antihyperglycemic agent MF can provide a new direction in the field of periodontal regeneration. However, long-term, multicenter, randomized, controlled clinical trials will be required to know its clinical, histologic, and radiographic effect on bone healing.

Disclosure

The author reports no conflicts of interest in this work.

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Figures

Figure (1) : Clinical Probing Depth at baseline.

Figure (2) : Clinical Probing Depth after 6 months

Tables

Time	PI (Mean±SD)	p-value
Baseline	1.75±0.72	0.872ns
6 months	0.38±0.50	0.028*
p-value	<0.001*	

Table 1: Plaque Index (PI) mean and standard deviation values assessed at baseline and 6 months.

Time	GI (Mean±SD)	p-value
Baseline	1.65±0.51	0.205ns
6 months	0.45±0.49	<0.001*
p-value	<0.001*	

Table 2: Gingival Index (GI) mean and standard deviation values assessed at baseline and 6 months

Time	PD (mm) (Mean±SD)	p-value
Baseline	7.20±1.13	0.283ns
6 months	3.25±0.49	<0.001*
p-value	<0.001*	

Table 3: Pocket Depth (PD) mean and standard deviation values assessed at baseline and 6 months.

Time	CAL (mm) (Mean±SD)	p-value
Baseline	5.60±0.80	0.551ns
6 months	3.70±0.62	<0.001*
p-value	<0.001*	

Table 4: Clinical Attachment Level (CAL) mean and standard deviation values assessed at baseline and 6 months.