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Efficacy of Topically Applied Metformin Gel 1% In Non-Surgical Treatment of Periodontitis Patients with Type 2 Diabetes Mellitus

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Abstract

Background: *Diabetes is a chronic metabolic disorder marked by hyperglycemia and is among the leading etiology of mortality globally among non-communicable illnesses.*

Aim: *To assess the effectiveness of 1% metformin gel as a non-surgical treatment for stage I and II Grade B periodontitis cases with Type 2 diabetes.*

Patients and methods*: This investigation was a split-mouth randomized controlled clinical, radiographic, and biochemical investigation conducted on fifteen cases with type 2 diabetes mellitus, stage I or II, grade B periodontitis, chosen from the outpatient clinic of the Oral Medicine and Periodontology Department at the Faculty of Dental Medicine, Al-Azhar University, Assiut Branch.*

Results: *In group I, the mean of malondialdehyde (MDA) baseline was 6.48, then decreased to 5.16 after two weeks, then increased to 6.09 after four weeks, while in group II, the mean of MDA baseline was 6.21, then decreased to 4.61 after two weeks, then increased to 4.99 after four weeks. In group I, the mean of High Mobility Group Box 1 (HMGB1) baseline was 953.06, then decreased to 756.17 after two weeks, then increased to 857.00 after four weeks, while in group II, the mean of HMGB1 baseline was 956.18, then decreased to 744.82 after two weeks, then increased to 776.15 after four weeks.*

Conclusion: *Diabetes-related periodontitis is linked to inflammation and oxidative stress. with metformin gel improving periodontal parameters, reducing inflammation, and promoting bone regeneration in diabetic patients.*

Key words: *Periodontitis; Diabetes; Metformin gel; MDA.*

Introduction

Diabetes is a chronic metabolic disorder marked by hyperglycemia and is among the primary causes of mortality globally among non-communicable illnesses [1].

Chronic periodontal illness ranks as the sixth most prevalent consequence of diabetes, exhibiting a bidirectional interaction with this chronic metabolic disorder, among the numerous end-stage problems correlated with type 2 diabetes [2].

Periodontal disorders are intricate, chronic inflammatory conditions that damage the supporting tissues of the periodontium. The deleterious pattern defining chronic periodontitis, which clinically manifests as a disease impacting the tooth-supporting tissues, is attributable to active connective tissue loss as well as progressive bone resorption induced by various stimulatory factors in plasma; these factors arise from the heightened reactive oxygen species (ROS) and respiratory burst of neutrophils [3].

The aim of this research was to assess the efficacy of 1% metformin gel as adjunctive non-surgical treatment in

stage I and II Grade B periodontitis cases with type 2 diabetes mellitus through: Primary outcome: The clinical and radiographic parameters. Secondary outcome: The level of HMGB1 & MDA in gingival crevicular fluid.

Patient and method:

This was a split-mouth randomized controlled clinical, radiographic, and biochemical investigation performed on fifteen cases with type 2 diabetes mellitus and stage I or II, Grade B periodontitis, chosen from the outpatient clinic of the Oral Medicine and Periodontology Department at the Faculty of Dental Medicine, Al-Azhar University, Assiut Branch.

Inclusion Criteria: Patients with controlled Type 2 Diabetes Mellitus (HbA1c < 7%) and patients with Stage I or II, Grade B periodontitis.

Exclusion Criteria: Cases under systemic metformin treatment, cases with systemic diseases affecting biomarkers or periodontal conditions and patients who had non-surgical periodontal treatment in the last 3 months, smokers and alcoholics, patients under antimicrobial therapy in the past month, immunosuppressed patients or those with allergic reactions to the study drugs and pregnant or lactating women.

Patients were randomly separated. into two groups using a coin toss: Group I: Involving 15 patients with Type 2 Diabetes Mellitus, both Stage I and II, underwent non-surgical periodontal treatment and placebo gel application. group II: Involving 15 patients with Type2 Diabetes Mellitus underwent non-surgical periodontal treatment and 1% Metformin in situ gel local delivery.'

Methods

Preparation of 1% Metformin Gel: Preparation Site: Research Laboratory, Faculty of Pharmacy, Minia University. Components: 1% metformin hydrochloride dissolved in purified water, Carbopol® 934 polymer for gel base, and triethanolamine (TEA) to adjust viscosity and ph. The gel was freshly prepared before each application and transported in an icebox at 4°C to the clinic.

Periodontal Intervention: Phase I Periodontal Therapy: Patient education, mechanical plaque control, correction of restorative factors, scaling, and root planning (SRP) using hand instruments and ultrasonic devices.

Intra-pocket Application: GCF sampling was conducted in the morning, with patients advised to avoid eating, drinking, brushing, or using mouthwash. Two sites per patient were selected for treatment: one control site with SRP + placebo gel and one experimental site with SRP + 1% metformin gel. The gel was injected into periodontal pockets, covered with periodontal dressing, and repeated at 2 weeks and 4 weeks after the initial treatment.

Periodontal Evaluation: Clinical evaluation: Periodontal parameters to monitor the development of illness and the effectiveness of the treatment. The following parameters were evaluated: Plaque Index (PI) [4], which measures plaque accumulation around the gingival margin; Gingival Index (GI) [5], which assesses the degree of gingival inflammation; Probing Pocket Depth (PPD) [6], which indicates the depth of periodontal pockets; and Clinical Attachment Level (CAL) [7], which reflects the extent of attachment loss. These parameters have been measured at baseline, one month, three months, and six months following the initial treatment. The evaluation was conducted using standardized clinical techniques, including the use of William's graduated periodontal probe for accurate measurements of PPD and CAL. The data collected provided a comprehensive assessment of the patients' periodontal health, allowing for the identification of improvements or deterioration over time. radiographic assessment focused on measuring the Marginal Bone Level (MBL), which was evaluated at baseline, 1, 3, and 6 months using dental X-ray imaging and Image J software for linear measurement analysis. This allowed for the tracking of bone loss or gain over time, providing insights into the efficacy of the treatment of periodontal tissue regeneration and biochemical evaluation, the concentrations of HMGB1 and Malondialdehyde (MDA) in the Gingival Crevicular Fluid (GCF) were measured. These biomarkers were assessed at baseline, 2, and 4 weeks to monitor inflammatory and oxidative stress responses during the treatment period. GCF samples were collected using absorbent paper points, ensuring precise sampling from the periodontal pockets. The collected samples were stored in Eppendorf tubes including phosphate buffer saline (PBS) and immediately frozen at -80°C to preserve their integrity until further analysis utilizing enzyme-linked immunosorbent assay (ELISA). This approach provided quantitative data on the levels of HMGB1 and MDA, which are critical indicators of periodontal disease activity and treatment outcomes.

Ethical consideration

The research has been permitted by the ethical committee, Faculty of Dental Medicine, Al-Azhar University (fig. 1). NO: AUAREC20220007-4. All cases were fully informed about the study's nature and the possible risks of the research procedures; they signed the consent form before work.

Statistical analysis:

The study involved revising and validating data using SPSS and analyzing it on an IBM-compatible PC. Descriptive statistics have been conducted for all factors in three groups, presented in various forms. Comparisons were made between independent and paired groups using independent t-tests, paired t-tests, and repeated measure ANOVAs. The level of significance was calculated using probability (P) values, with $P > 0.05$ indicating non-significant, $P < 0.05$ indicating significant, and $P < 0.001$ indicating highly significant. The results were presented in the form of mean, standard deviation, median, maximum, minimum, percentages, and range.

Results:

Table 1 illustrated that there were 10 (66.6%) cases that were female and 5 (33.3%) cases that were male, and the age ranged from 30 to 64 years with a mean of 45.33 years.

Table 2 illustrated that, in group I, the mean of Plaque Index baseline was 1.87, then decreased to 0.58 after one month, then increased to 0.63 after three months, then increased to 0.88 after six months, while in group II the mean of PI baseline was 1.89, then decreased to 0.46 after one month, then increased to 0.54 after three months, then increased to 0.67 after six months.

Table 3 illustrated that, in group I, the mean of the Gingival Index baseline was 1.87, then decreased to 0.57 after one month, then increased to 0.64 after three months, then increased to 0.83 after six months, while in group II, the mean of the GI baseline was 1.87, then decreased to 0.47 after one month, then increased to 0.54 after three months, then increased to 0.65 after six months.

Table 4 illustrated that, in group I, the mean of PD baseline was 4.00, then decreased to 2.87 after one month, then increased to 3.00 after three months, then increased to 3.20 after six months, while in group II, the mean of PD baseline was 4.07, then decreased to 2.33 after one month, then increased to 2.35 after three months, then increased to 2.40 after six months.

Table 5 illustrated that, in group I, the mean of CAL baseline was 3.00, then decreased to 2.13 after one month, then increased to 2.27 after three months, then increased to 2.40 after six months, while in group II, the mean of CAL baseline was 2.93, then decreased to 1.47 after one month, then increased to 1.80 after three months, then increased to 2.07 after six months.

Table 6 illustrated that, in group I, the mean of MDA baseline was 6.48, then decreased to 5.16 after two weeks, then increased to 6.09 after four weeks, while in group II, the mean of MDA baseline was 6.21, then decreased to 4.61 after two weeks, then increased to 4.99 after four weeks.

Table 7 illustrated that, in group I, the mean of HMGB1 baseline was 953.06, then decreased to 756.17 after two weeks, then increased to 857.00 after four weeks, while in group II, the mean of HMGB1 baseline was 956.18, then decreased to 744.82 after two weeks, then increased to 776.15 after four weeks.

Table 8 illustrated that, in group I, the mean of MBL baseline was 3.03, then decreased to 2.98 after one month, then decreased to 2.87 after three months, then decreased to 2.62 after six months, while in group II, the mean of MBL baseline was 3.06, then decreased to 2.91 after one month, then decreased to 2.70 after three months, then decreased to 2.35 after six months.

Table 1 Distribution of the studied cases according to Sex and Age

		No. = 15
Sex	Female	10 (66.6%)
	Male	5 (33.3%)
Age	Mean ± SD	45.33 ± 13.26
	Range	30 − 64

Table 2 Comparative analysis among Group I and Group II according to PI Score at different intervals

PI		Group I	Group II	Test value•	P-value	Sig.
		Number = 15	Number = 15			
Baseline	Mean ± SD	1.87 ± 0.28	1.89 ± 0.20	-0.187	0.853	NS
	Range	1.55 – 2.56	1.55 – 2.28			
After one month	Mean ± SD	0.58 ± 0.13	0.46 ± 0.11	2.565	0.016	S
	Range	0.43 – 0.85	0.34 – 0.67			
After three months	Mean ± SD	0.63 ± 0.12	0.54 ± 0.11	1.990	0.046	S
	Range	0.46 – 0.92	0.41 – 0.73			
After six months	Mean ± SD	0.88 ± 0.22	0.67 ± 0.09	3.383	0.002	HS
	Range	0.69 – 1.3	0.56 – 0.85			

P-value >0.05: Non significant (NS); P-value <0.05: Significant(S); P-value< 0.01: highly significant (HS); •: Independent t-test

Table 3 Comparative analysis among Group I and Group II according to GI Score at different intervals

GI		Group I	Group II	Test value•	P-value	Sig.
		Number = 15	Number = 15			
Baseline	Mean ± SD	1.87 ± 0.23	1.87 ± 0.20	-0.042	0.967	NS
	Range	1.55 – 2.25	1.6 – 2.25			
After one month	Mean ± SD	0.57 ± 0.15	0.47 ± 0.11	2.223	0.034	S
	Range	0.43 – 0.85	0.34 – 0.67			
After three months	Mean ± SD	0.64 ± 0.14	0.54 ± 0.10	2.240	0.033	S
	Range	0.46 – 0.92	0.41 – 0.7			
After six months	Mean ± SD	0.83 ± 0.14	0.65 ± 0.14	3.550	0.001	S
	Range	0.66 – 1.08	0.46 – 0.97			

Table 4 Comparative analysis among Group I and Group II according to PPD in mm at different intervals

PD		Group I	Group II	Test value•	P-value	Sig.
		Number = 15	Number = 15			
Baseline	Mean ± SD	4.00 ± 0.85	4.07 ± 0.80	-0.222	0.826	NS
	Range	3 – 5	3 – 5			
After one month	Mean ± SD	2.87 ± 0.74	2.33 ± 0.49	2.323	0.028	S
	Range	2 – 4	2 – 3			
After three months	Mean ± SD	3.00 ± 0.65	2.35 ± 0.50	3.162	0.004	HS
	Range	2 – 4	2 – 3			
After six months	Mean ± SD	3.20 ± 0.77	2.40 ± 0.74	2.898	0.007	HS
	Range	2 – 4	1 – 4			

Table 5 Comparative analysis among Group I and Group II according to CAL in mm at different intervals

CAL		Group I	Group II	Test value•	P-value	Sig.
		Number = 15	Number = 15			
Baseline	Mean ± SD	3.00 ± 0.85	2.93 ± 0.88	0.211	0.834	NS
	Range	2 − 4	2 − 4			
After one month	Mean ± SD	2.13 ± 0.74	1.47 ± 0.64	2.633	0.014	S
	Range	1 − 3	1 − 3			
After three months	Mean ± SD	2.27 ± 0.96	1.80 ± 0.56	1.624	0.026	S
	Range	1 − 4	1 − 3			
After six months	Mean ± SD	2.40 ± 0.63	2.07 ± 0.80	1.267	0.046	S
	Range	1 − 3	1 − 3			

Table 6 Comparative analysis among Group I and Group II according to MDA level at GCF in nanogram at different intervals

MDA		Group I	Group II	Test value•	P-value	Sig.
		Number = 15	Number = 15			
Baseline	Mean ± SD	6.48 ± 0.92	6.21 ± 0.74	0.868	0.393	NS
	Range	5.4 − 8.1	5.2 − 7.6			
2 weeks	Mean ± SD	5.16 ± 0.76	4.61 ± 0.75	1.998	0.065	NS
	Range	4.1 − 7.36	3.2 − 6			
4 weeks	Mean ± SD	6.09 ± 0.65	4.99 ± 0.54	5.056	0.000	HS
	Range	5.3 − 7.57	4 − 6.3			

Table 7 Comparative analysis among Group I and Group II according to HMGB1 level at GCF in nanogram at different intervals

HMGB1		Group I	Group II	Test value•	P-value	Sig.
		Number = 15	Number = 15			
Baseline	Mean ± SD	953.06 ± 145.99	956.18 ± 143.82	-0.059	0.953	NS
	Range	785.7 − 1281.1	808.6 − 1230.5			
2 weeks	Mean ± SD	756.17 ± 121.72	744.82 ± 120.05	0.257	0.799	NS
	Range	523.9 − 909.6	621.3 − 980.4			
4 weeks	Mean ± SD	857.00 ± 70.52	776.15 ± 107.40	2.437	0.021	S
	Range	762.7 − 974.5	638.1 − 945.2			

Table 8 Comparative analysis among Group I and Group II according to MBL in mm at different intervals

MBL		Group I	Group II	Test value•	P-value	Sig.
		Number = 15	Number = 15			
Baseline	Mean ± SD	3.03 ± 0.47	3.06 ± 0.42	-0.166	0.869	NS
	Range	2.4 − 3.8	2.37 − 3.82			
After one month	Mean ± SD	2.98 ± 0.47	2.91 ± 0.47	0.400	0.692	NS
	Range	2.35 − 3.71	2.28 − 3.79			
After three months	Mean ± SD	2.87 ± 0.47	2.70 ± 0.44	0.994	0.329	NS
	Range	2.16 − 3.65	1.97 − 3.53			
After six months	Mean ± SD	2.62 ± 0.35	2.35 ± 0.37	2.060	0.369	S
	Range	1.94 − 3.27	1.54 − 2.95			

Discussion

At present study, it showed that, as regards the age, patients included in the present work ranged in age between 30-64 years old. This age range matches with recent studies emphasize the strong epidemiological link between

diabetes and periodontitis, particularly noting that age is a key factor influencing this association. Diabetic patients are more susceptible to periodontitis, which can worsen with age, impacting both oral and systemic health. Evidence suggests that individuals over 55 face heightened risks of periodontal disease, which can exacerbate complications from diabetes, including cardiorenal conditions and mortality rates.
Additionally, a younger diabetic adult (ages 35-54) with stage I, II periodontitis show significantly increased mortality risk from heart and kidney disease compared to those with mild or no periodontal issues [8,9].
Regarding the plaque accumulation and degree of gingival inflammation, the results of the present study found statistically significant reduction in PI and GI scores of both groups at different intervals when compared to baseline without significant differences between both groups in the GI and PI at the observation period. These results may be explained by that, oral hygiene was maintained and reinforced in all patients during the observation period of the study. Also, attributed to the study design itself which eliminates inter-subject variance. This is in agreement to the findings of the study which concluded that, the application of MET gel 1% following conventional therapy for periodontitis contributes to improve clinical parameters[10,11].
These results align with other study which reported similar GI reductions over the same period. Metformin's anti-inflammatory properties likely contributed to these outcomes, consistent with findings on host modulators like probiotics and anti-inflammatory agents[12,13].
Both groups in the present study experienced significant reductions in PI and GI at various intervals, with highly significant reductions in Group II noted at six months. While metformin group at our study consistently aligned most parameters with antioxidant adjuncts (e.g., melatonin, grape seed extract) which showed significant reductions in PI and GI, but with varying magnitudes depending on the specific antioxidant. Comparable reductions were noted, particularly with antioxidants like alpha-lipoic acid and grape seed extract, indicating shared therapeutic benefits with metformin gel 1%[14].
The present study demonstrated significant reductions in PD in both the control and metformin groups at one and three months, with the effect remaining significant until six months. This may be attributed to that MET suppresses Matrix metalloproteinase MMP-1, MMP-2, MMP-8 and IL-8 in LPS-stimulated human gingival fibroblasts suggesting a potential positive impact on gingival cells reducing inflammation and extracellular matrix degradation [15]. The metformin group showed a highly significant (HS) reduction in PD at three and six months, particularly in deeper pockets. These findings are consistent with different clinical studies [11,18] that demonstrated the efficacy of 1% metformin gel in reducing PD in patients with moderate and severe chronic periodontitis. Another study similarly reported a significant reduction in PD at six months for the metformin group [13]. Compared to a systematic review which found a weighted mean PD reduction of ~2.12 mm favoring metformin gel, our study achieved slightly greater reductions (2.40 mm in the metformin group versus 3.20 mm in the control group at six months), reinforcing metformin's effectiveness [16].
The current study revealed significant CAL improvements in the metformin group at one, three and six months. Indicating an advantage of metformin gel application on CAL. The prolonged effects of metformin gel on the periodontal ligament and clinical attachment levels are attributed to the direct action of MET on gingival fibroblast which promote and accelerate collagen deposition, increases the density of the periodontal ligament, induces bone turnover and neovascularization with increased expression of growth factors besides connective tissue formation on the root surface, formation of dense fibers bound to the alveolar bone and newly synthesized cementum in teeth[17]which aligns with other studies[13,18,19] corroborated our findings at baseline, the CAL in Group II was 2.93 ± 0.88 mm, which reduced to 2.07 ± 0.80 mm after six months, with statistically significant differences ($p = 0.046$).
Present study recorded a steady improvement in MBL over time (from 3.06 mm to 2.35 mm) over six months, compared to 2.62 mm in the control group. These reductions were statistically significant across all intervals, which attributed to MET direct influence on osteoblasts promotes their differentiation and activity, leading to increased bone matrix production. This effect is primarily mediated through the activation of the AMP-activated protein kinase (AMPK) pathway, which subsequently upregulates bone morphogenetic proteins (BMPs) essential for bone growth[20].Also, Inhibition of Osteoclast Formation and Activity dual action stimulating osteoblasts while inhibiting osteoclasts favors a net increase in bone density and supports the maintenance of marginal bone levels around teeth[21]which reflect a significant gain in MBL after 6 months in group II than group I, this significance can be explained as the newly formed bone maturation need 6-8 months after treatment

that can be detected radiographically[17].

In contrast, Nicolini's study reported a weighted mean difference of approximately 2 mm favoring the metformin group after 6 months, indicating a more pronounced improvement in MBL compared to controls. While both studies demonstrated the beneficial effects of metformin as an adjuvant therapy, the degree of improvement was greater in Nicolini's findings. This discrepancy could stem from differences in study design, sample size, or baseline MBL values [19].

Biochemically, HMGB1 demonstrated that there were non statistical significant between Group I and Group II regarding HMGB1 Baseline and after two weeks, while there were statistical significant after four weeks.

Metformin's ability to bind HMGB1 reduces its inflammatory action, which could be particularly beneficial in diabetic patients who are more susceptible to periodontitis due to higher baseline inflammation and altered immune response. Studies have also demonstrated that metformin-loaded nanoparticles targeting periodontal pockets decrease inflammation and support bone retention, further validating its adjunct role in periodontal therapy for diabetes-associated periodontitis [21].

One study on the effect of periodontal treatments showed that levels of HMGB1 in GCF decreased after treatment, underscoring the role of HMGB1 in inflammation and tissue damage in periodontal disease [22].

For MDA, control group showed a baseline mean of 6.48 ± 0.92 ng, which significantly decreased to 5.16 ± 0.76 ng after two weeks but rise again to 6.09 ± 0.65 ng at the four-week mark, indicating a transient reduction in oxidative stress. Conversely, the metformin group exhibited a baseline mean of 6.21 ± 0.74 ng, which markedly decreased to 4.61 ± 0.75 ng after two weeks and showed a minimal increase to 4.99 ± 0.54 ng after four weeks, indicating a reduction in oxidative stress due to metformin's antioxidant effects which has been found to reduce lipid peroxidation in cardiovascular conditions and diabetes by activating the AMPK pathway, which can indirectly reduce MDA and improve inflammatory profiles. Given this mechanism, metformin might similarly impact MDA in GCF directly [23,24].

Conclusion

The adjunctive use of 1% metformin gel provides significant benefits to clinical periodontal outcomes when combined with mechanical periodontal therapy in type II diabetic patients with stage I and II periodontitis. This localized drug delivery method not only reduces marginal bone loss over a six-month period but also demonstrates anti-inflammatory and antioxidant effects by significantly lowering levels of malondialdehyde (MDA) and high-mobility group box-1 (HMGB1).

Recommendation

The study suggests using 1%. metformin gel as an adjunctive treatment for diabetic patients with periodontitis to improve clinical outcomes. It emphasizes the importance of oral hygiene and regular periodontal care to reduce inflammation and systemic complications. Monitoring HMGB1 and MDA as diagnostic and therapeutic indicators is also suggested. Further research is needed to optimize metformin gel concentrations and assess its efficacy in diverse patient populations.

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