Local effect of metformin gel (1%) as an adjuvant in the periodontal treatment of patients with type II diabetes mellitus with periodontitis: A Double-blind randomized clinical trial

ABSTRACT

Aims: The aim of this study was to evaluate the efficacy of 1% metformin gel administered locally as an adjunct to basic periodontal treatment in patients with periodontitis at different stages, with type II diabetes mellitus, who were using oral metformin.
Study design: This is a randomized, parallel, double-blind, clinical and laboratory-based clinical study.
Place and Duration of Study: It was carried out from April 2022 to March 2023. Study carried out in Cascavel-PR, Brazil.
Methodology: Total of 39 patients were evaluated, divided into two groups, CM (n=20): Periodontal therapy with an association of 1% metformin gel and SM (n=19): Periodontal therapy with placebo gel association. The patients were evaluated at 0, 3 and 6 months, through the following exams: clinical exams (clinical probing depth, bleeding on probing, clinical attachment loss and plaque index), hematological exams (fasting glucose, glycosylated hemoglobin, creatinine and total cholesterol and fractions) and collection of gingival crevicular fluid for evaluation of IL-17 by means of the ELISA test and to determine the amount of fluid absorbed (mm2).
Results: Both groups significantly reduced the amount of plaque, bleeding on probing and the amount of gingival crevicular fluid in mm2 ($p<0.05$) while CPD (clinical probing depth)was significantly reduced ($p<0.05$) only in the CM group. When evaluating the different probing depths, pockets <5 and ≥ 5 mm reduced significantly ($p<0.05$) in the CM group, while in the SM group, only pockets <5 mm were significantly reduced. The results of the hematological exams did not show statistical difference in this period and the same occurred with the amount of IL-17 present in the gingival crevicular fluid.
Conclusion: According to the results obtained in the present study, the local application of 1% metformin gel in patients with PD and type II DM was effective when associated with basic periodontal treatment over periodontal clinical parameters, compared to the placebo gel.

Keywords: Diabetes Mellitus type II, Periodontitis, Metformin, Periodontal Disease.

1. INTRODUCTION

Diabetes mellitus (DM) is considered one of the main risk factors for periodontitis (PD). Individuals with decompensated diabetes are more likely to have PD of increased severity, and PD is now considered a complication of diabetes. It is not only glycemic control

that is related to periodontal disease (PD), but also microvascular complications that show associations with severe periodontitis [1].

The main types of DM are type I and type II. Type I diabetes (DMI) is characterized as an autoimmune disorder that affects pancreatic cells [2] resulting in progressive insulin deficiency [3], while type II (DMII) is the result of pancreatic beta cell damage that impairs the ability to use insulin. DM has several associated complications, as high blood sugar damages organs and tissues throughout the body. The longer the body deals with high blood sugar levels, the risk of further complications increases. These complications can be microvascular, such as nephropathy, retinopathy, loss of vision and macrovascular, such as heart disease, heart attack, stroke and neuropathy, infections and wounds with decreased healing process, bacterial and fungal infections, depression, and dementia [2].

Glycemic control is directly involved in the onset and worsening of diabetic complications, such as PD, because high glucose increases the formation of AGEs (advanced glycation end products), which in turn play an important role in the pathogenesis of these complications [4]; [5]; [6]. AGEs are basically the binding of glucose to a protein and the most common example is glycosylated hemoglobin (HbA1c), used to diagnose DM. Once this bond is formed, AGEs become irreversible and remain bound throughout their half-life. In the body, AGEs interact directly with collagen, forming stable collagens that are resistant to normal enzymatic degradation, so they can generate tissue changes and undegraded collagens accumulate to form atheroma in small and large vessels [6].

PD is a chronic inflammatory disease that begins with the accumulation of pathogenic dental biofilm above and below the gingival margin, leading to microbial dysbiosis and a destructive inflammatory response [7]. It is characterized by host-mediated inflammation associated with microorganisms that result in the loss of periodontal attachment [8].

Diabetes has a negative effect on periodontal health and this, in turn, affects glycemic control and increases the occurrence of complications. Effective periodontal therapy can help improve blood glucose levels in patients with DM, and improved blood glucose control can decrease the risk of PD onset and development [9].

There is no consensus on which periodontal treatment is best suited to diabetic patients, however, non-surgical treatment through scaling and root planing is considered the traditional treatment. It involves a series of appointments at intervals of a week or more, where each appointment usually involves scaling and root planing by quadrant or sextant, depending on the severity of the disease. It is known that the success of this traditional treatment is related to the reduction of periodontal pathogens, favoring the increase of beneficial bacteria [10].

Metformin (MF) is one of the most widely used oral antihyperglycemic agents for the treatment of DMII. It is currently recommended as first-line therapy in overweight or obese patients with this condition. It is a second-generation biguanide, with the ability to lower blood glucose levels and consequently the liver's production of glucose. Its main mechanism of action is its action on hepatocytochondria, where it interferes with intracellular calcium handling, decreasing gluconeogenesis and increasing the expression of glucose transporters, which in turn leads to a decline in hepatic glucose production and a decrease in peripheral insulin resistance. Thus, promoting a reduction in blood glucose levels [11]; [12]; [13].

MF also has anti-inflammatory properties and inhibits IL-1β-induced activation of inflammatory pro-phosphokinases. This drug has been shown to improve alkaline phosphatase activity in the MC3T3E1 osteoblasts type and helps collagen production (type 1) in the UMR106 and MC3T3E1 cell types, thus facilitating osteoblast differentiation and bone formation. Therefore, by facilitating osteoblasts differentiation, this drug may exhibit a favorable effect on alveolar bone in PD [14].

In fact, it has been shown that the greatest benefit of MF in periodontal therapy is related to a reduction in clinical probing depth (CPD) and gain in clinical attachment level (AL), greater than the control groups, without MF [15].

Despite the progressive development of research associating MF gel with PD treatment, there is still a scarce number of studies investigating the response of this gel in patients with systemic alterations, such as DM. Studies by Pradeep, *et al*. (2013), Pradeep, *et al*. (2017) and Kurian, *et al*. (2018) showed significantly better results in the groups receiving metformin gel (MG) [12]; [16]; [17]. However, volunteers with DM or immunocompromised were excluded from the study.

The aim of this study was to evaluate the effect of MF gel 1% administered locally as an adjunct to basic periodontal treatment in PD patients at different stages with DMII.

2. MATERIAL AND METHODS

Study design:

This is a randomized, quantitative, clinical and laboratory-based, double-blind, parallel to analyze the action of MF gel 1% associated with the treatment of PD in patients with DMII who use systemic MF, seen at the outpatient clinic of the University Hospital of Western Paraná (HUOP) and Intermunicipal Health Consortium of Western Paraná (CISOP) in Cascavel-PR.

The patients examined in this study were only those previously diagnosed and classified as having the pathophysiological condition of DMII by endocrinologists in the city of Cascavel-PR and who were taking systemic MF.

In addition to the clinical examination, the gingival crevicular fluid (GCF) was collected, and the health history analyzed, considering the possible association of MF in helping to control PD.

Patient selection:

The groups were made up of patients aged between 18 and 70, seen at the Endocrinology outpatient clinic of HUOP and CISOP in the city of Cascavel-PR, diagnosed with DMII (confirmed by endocrinologists) and taking oral MF.

Sample calculation:

To calculate the sample size, the number of patients is based on the application of the T-Test for independent samples, with a test power of 80% and a significance level of 5%, these data being based on a previous study (ZAMPIVA *et al*., 2019), with a minimum sample of 36 patients [18]. For this study, a total of 39 patients were assessed.

Data collection method:

Inclusion criteria:

- Patients of both sexes with PD stages 1, 2, 3 or 4, grade B or C, presenting bleeding on probing (BOP) and gingival inflammation[8].
- Patients must have the pathophysiological condition of DMII (diagnosed by endocrinologists) and be taking systemic MF.
- Patients who agree to take part in the study by signing the free and informed consent form.

Exclusion criteria:

- Patients with a positive history in the last six months of broad-spectrum antibiotic therapy, steroidal anti-inflammatory drugs or immunosuppressive therapy in the three months prior to the study.

- Pregnant or lactating women.
- History of periodontal treatment in the last six months.
- Smoking or quitting less than five months previously.
- Patients with fewer than four teeth or misaligned teeth.

Clinical examination and periodontal treatment:

The clinical examination was carried out by a previously trained examiner and in suitable ergonomic and lighting conditions for intra- and inter-examiner repetition in relation to the positioning and inclination of the millimeter probe, as well as in relation to the probing pressure (which should be approximately 25 grams). The initial periogram(clinical periodontal examination) was carried out, and gingival crevicular fluid (GCF) was collected to analyze the amount of fluid and interleukin 17 (IL-17), as well as laboratory tests (baseline).

After the initial clinical examination, a previously trained team carried out basic periodontal treatment including guidance and motivation on oral hygiene (modified Bass technique and flossing), supra- and subgingival scaling, root planing and coronal polishing. All patients received the same oral hygiene guidance, as well as supportive therapy, over a period of 3 and 6 months. 2g of amoxicillin as antibiotic prophylaxis one hour before the appointment was prescribed for all patients [19].

Randomization and blinding:

The patients were randomly assigned to 2 groups: group 1 with the association of metformin gel –metformin presence - (**MP**) and group 2 without the association of metformin, using a placebo gel – metformin absence (**MA**).

The gels were identical in texture, color and taste, prepared in two identical bottles, identified only as group 1 (G1) and group 2 (G2):

G1 = MP (n 20): Patients with PD stages 1, 2, 3 or 4, grade B or C with DMII using oral MF and association of GM 1% in periodontal therapy.

G2 = MA (n 19): Patients with PD stages 1, 2, 3 or 4, grade B or C, with DMII using oral MF, without the association of GM 1% in periodontal therapy.

In the MP group, sites equal to or larger than 4 mm of CPD were treated with 1% GM injected into the periodontal pocket using a Luer-Lock syringe (10 ml), the gel was applied until it filled the entire length of the pocket. In the MA, the placebo gel (without the addition of metformin) it was also placed using a Luer-Lock syringe (10 ml) directly into periodontal pockets with a CPD equal to or greater than 4 mm, and all applications were carried out under relative isolation. Patients were instructed not to chew hard or adhesive food. After seven days, the patients returned to an appointment and any supragingival deposits were removed, after which time the patients were allowed to normally clean the areas where the gel had been applied. After 3 and 6 months, all patients were re-evaluated and a new periogram was carried out, GCF was collected to analyze the amount of fluid and IL-17, as well as laboratory tests.

Parameters assessed:

In sequential order and out of convenience, the following were evaluated:

Clinical probing depth (CPD): Distance from the gingival margin (GM) to the bottom of the sulcus/pocket with presence or absence recorded and measured in millimeters.

Bleeding on probing (BOP): Every three teeth, with an interval of approximately 30 seconds, to record the parameter corresponding to probing time, with presence or absence recorded.

Clinical loss of insertion (CLI): Distance from the cement-enamel junction (CEJ) to the bottom of the sulcus/pocket, with presence or absence recorded and measured in millimeters. It is obtained from the sum of gingival recession (GR) and CPD, as follows: (PCI = GR + CPD) - a method used in large epidemiological studies, such as the National Health and Nutrition Examination Survey (NHANES) and a recent clinical study [20].

Plaque Index (PI): The O'Leary Index is used to count dental biofilm, which makes it easier for individuals to visualize their brushing deficiencies, thus serving as motivation. The index consists of counting the visible biofilm, by cheek, of all the teeth present [21].

Tooth groups and sites evaluated:

For both groups, the teeth must be aligned in the dental arch, with at least four teeth present, where six sites per tooth were assessed, being: mesiobuccal, buccal and distobuccal; mesiolingual, lingual and distolingual.

Hematological tests for analysis:

The following tests were requested or collected from the University Hospital's electronic medical record (Tasy):

- Fasting blood glucose
- Glycosylated hemoglobin (HbA1c)
- Creatinine
- Total cholesterol
- HDL
-LDL

Diagnosis of insulin resistance*:*

Insulin resistance was assessed using the model described by the Brazilian Diabetes Society guidelines (2015-2016), using a Body Mass Index (BMI) greater than 28.9. The online calculator of the Federal University of Pelotas (UFPEL) was used to calculate BMI.

Quantification of cytokines in GCF:

GCF collection

Four sites were selected from different teeth, on the buccal and lingual/palatal surfaces, with gingival inflammation and higher CPD detected previously. Stagnant sulcular fluid was collected by inserting a sterile absorbent paper cone held for 30 seconds into the selected sites, disposing samples contaminated with blood. The cones containing the fluid from sites with the same characteristics for each patient were packed in a single sterile *eppendorf* tube and stored at -80°C.

IL-17 measurement using the Elisa test

The samples previously collected on absorbent paper and frozen at -80°C were thawed and then 500 µL of phosphate-buffered saline (PBS) was added to each tube and left to stand for 10 minutes. The samples were then centrifuged at 10000 rpm at 4°C and the cytokine was measured in the supernatant.

The Human IL-17 ELISA kit (Merck® RAB0262) was used to measure IL-17. The sensitized with human anti-IL17 antibody plate and the reagents were removed from the refrigerator and kept at room temperature for the assay. Briefly, 100 µL of sample or standard were pipetted into each well and incubated at room temperature for 2.5 hours. After this, the wells were washed four times with washing buffer supplied by the manufacturer, then previously diluted detection antibody was added, and the plate was incubated again at room temperature for 1 hour under agitation.

After the last incubation, the wells were washed again and then 100 µL of previously diluted streptavidin was added according to the manufacturer's instructions, and the plate was incubated for 45 minutes at room temperature under agitation. Then the wells were washed again with wash buffer, and 100 µL of the one-step TMB substrate solution supplied by the manufacturer was added to each well. The plate was incubated for 30 minutes in the dark. After the stop solution adding to each well, the plate was read on a plate reader (Biotek®) at a wavelength of 450 nm.

The absorbances were calculated after the standard curve calculating, and then the data was plotted in the GraphPad Prism 8.0.2 program and analyzed through the Two-way anova analysis of variance.

Quantification of absorbed GCF in mm^2:

GCF were collected from the same four sites selected in the previous analysis, using an absorbent paper cone. The supragingival plaque was carefully removed. After the sites had been isolated with cotton rolls and dried, the paper cones were inserted below the gingival margin for 30 seconds and immediately placed in a 0.2% alcoholic solution of ninhydrin (2,2-dihydroxyhydrindene-1,3-dione) for one minute. After drying, the cones were photographed in a standardized way and analyzed through a software (Image Pro Plus® 4.5.0.29, Media Cybernetics, Silver Spring, MD, USA) to determine the amount of fluid absorbed in mm^2 (LAGOS *et al*., 2011).

Statistical analysis:

The quantitative variables were assessed for the assumption of normality (Shapiro-Wilk test). In cases where the assumption was met, the ANOVA test was applied, followed by the Tukey test. In cases where the data had a non-normal distribution, a comparison was made using the non-parametric Kruskall-Wallis test followed by the Dun post-test, to compare the means for the 0-, 3- and 6-month periods within the same group, in order to assess whether or not there had been an improvement in the parameters. All the data was statistically analyzed using the statistical program Bioestat@ - version 5.3 (Sustainable Developmente Institute Mamirauá, AM, Brazil). A significance level of 5% was adopted for all tests.

3. RESULTS AND DISCUSSION

Between April 2022 and March 2023, 65 patients with DMII were examined. After the inclusion and exclusion criteria having been applied, 46 patients were included in the study; seven out of these dropped out during treatment, and a total of 39 patients were evaluated (Figure 1). No adverse effects or discomfort were reported in any group.

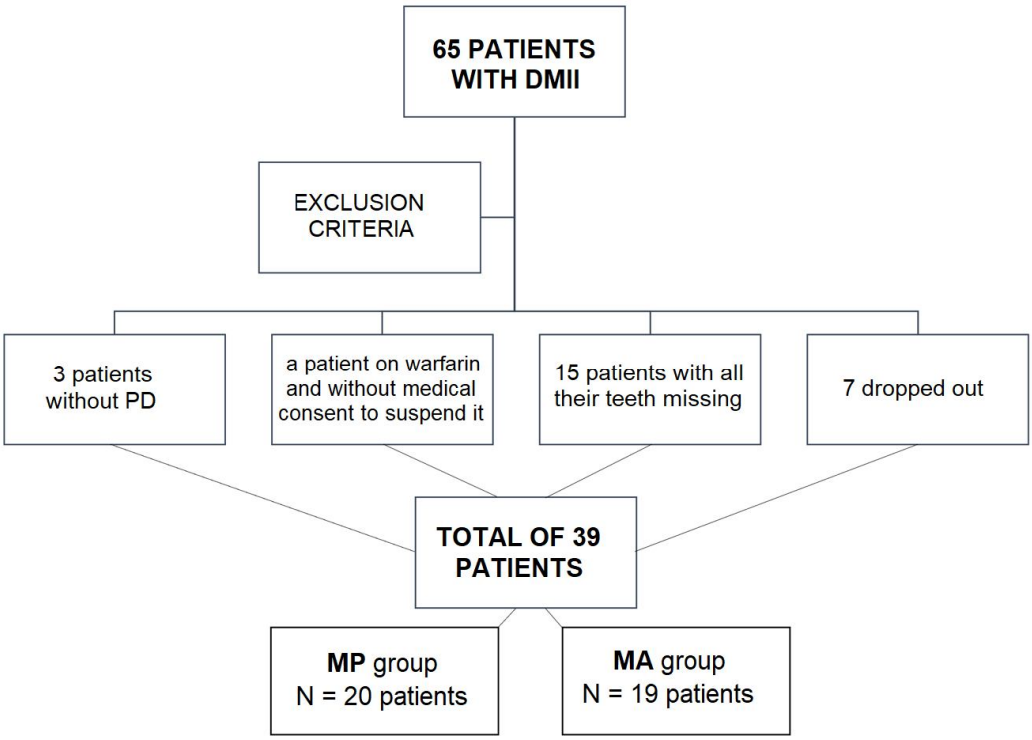

**Figure 1: Selection of patients after applying the exclusion criteria.*

Among the thirty-nine patients who completed the study, 46.15% were women and 53.85% men, evenly distributed between the groups, with a mean age of 53.3 years in the MP group and 55.8 years in group 2 in the MA group (Table 1). Regarding the BMI, 74.35% of the patients were diagnosed with insulin resistance (BMI > 28.9).

All patients tolerated the gel well, with no complications or adverse reactions. The soft tissues healed within normal limits and no significant visual differences were observed.

Groups	**Age**	**Weight**	**Height**	**Sex**	
MP	53.3 ± 11.2	90.2 ± 17.2	1.66 ± 0.08	**F**	9
				M	11
MA	55.8 ± 10.5	87.1 ± 16.2	1.66 ± 0.11	**F**	9
				M	10
p-value	**0.4781**	**0.5764**	**0.9879**		

**Table 1 - Anthropometric data of patients with DM*

Both groups significantly reduced the amount of plaque and BOP over the 6-month period, however CPD was significantly reduced only in the MP group. Although CLI was reduced in both groups, it was not statistically significant (Table 2).

Groups		BOP (%)	CPD (mm)	CLI (mm)	PI (%)
MP	**0**	23.3 ± 24.2 A	2.3 ± 0.6 A	2.8 ± 0.9	83.7 ± 26.5
	3 months	9.5 ± 9.5 B	2.2 ± 0.6 AB	2.8 ± 1.0	48.2 ± 23.5 #
	6 months	5.8 ± 5.6 B	1.8 ± 0.5 B	2.4 ± 0.8	26.3 ± 24.5 #
	p-value	**p<0.05**	**p<0.05**	**0.3246**	**p<0.05**
MA	**0**	17.7 ± 12.8 *	1.9 ± 0.4	2.3 ± 0.7	77.8 ± 22.9 A
	3 months	9.9 ± 8.7 *#	1.9 ± 0.3	2.2 ± 0.7	47.3 ± 30.9 B
	6 months	9.4 ± 8.9 #	1.7 ± 0.4	2.0 ± 0.7	37.4 ± 33.5 B
	p-value	**p<0.05**	**0.5748**	**0.5272**	**p<0.05**

**Table 2 -Clinical periodontal parameters of patients with DMII in both groups at 0, 3 and 6 months. Data expressed as mean ± standard deviation*
**Different letters, statistically significant data. ANOVA test followed by Tukey's post-test (p<0.05).*
#, statistically significant data. Kruskal-Wallis test followed by Dun's post-test (p<0.05).

When assessing the number of sites with different probing depths, it was possible to see that in the MP group there was a significant decrease in the number of pockets < 5mm and ≥ 5mm after 6 months, while in the MA group there was a significant decrease only in the number of pockets < 5mm in this same period (Table 3).

Groups		Pockets < 5 mm	Pockets ≥ 5 mm
MP	**0**	10.75 ± 13.6 [3.0-11.75] *	5.18 ± 6.0 [0-6.75] *
	3 months	4.75 ± 5.5 [0-7.0] *, #	2.93 ± 3.6 [0-4.75] *, #
	6 months	2.3 ± 3.0 [0-3.0] #	1.8 ± 2.7 [0-5.0] #
	p-value	**p<0.05**	**p<0.05**
MA	**0**	5.68 ± 5.9 [1,25-9,0] *	2.0 ± 4.2 [0-2.75]
	3 months	2.42 ± 2.6 [0,25-4,0] *, #	0.53 ± 0.8 [0-1.75]
	6 months	1.78 ± 2.2 [0-2,75] #	0.28 ± 0.6 [0-0.75]
	p-value	**p<0.05**	**0.2515**

** Table 3 – Number of sites with pockets < 5 mm and ≥ 5 mm in patients with Diabetes Mellitus in both groups at 0, 3 and 6 months. Data expressed as mean ± standard deviation (interquartile range)*
** *, #, Statistically significant data. Kruskal-Wallis test followed by Dun's post-test (p<0.05).*

When the amount of GCF per mm^2 was assessed, a significant reduction in fluid was observed in both groups after 6 months (Table 3). As for the IL-17 cytokine present in the GCF, there was no significant reduction in either group (Table 4 and Figure 2).

Groups		GCF (mm²)	IL-17 (mm²)
MP	**0**	783.3 ± 394.4 A	410.6 ± 7.2
	3 months	360.8 ± 200.6 B	410.9 ± 7.9
	6 months	236.9 ± 129.1 B	417 ± 9.8
	p-value	**p<0.01**	**0.2951**
MA	**0**	817.4 ± 363.8 A	415.9 ± 20.5
	3 months	352.7 ± 134.2 B	409.1 ± 4.0
	6 months	271.5 ± 74.4 B	422.7 ± 23.9
	p-value	**p<0.01**	**0.5506**

** Table 4 - Amount of GCF in mm^2 and expression of IL-17 in the GCF of patients with DMII in both groups at 0, 3 and 6 months. Data expressed as mean ± standard deviation*
** Different letters, statistically significant data. ANOVA test followed by Tukey's post-test (p<0.01).*

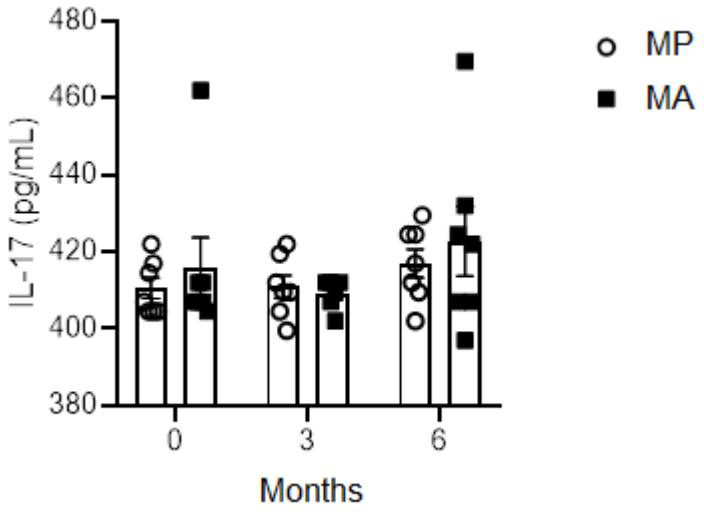

**Figure 2: Graph of IL-17 expression in the GCF of patients with DMII in both groups at 0, 3 and 6 months. Data expressed as mean ± standard deviation.*

There was no significant change in any of the blood parameters assessed in both the MP and MA after 6 months (tables 5 and 6).

Groups		Fasting Glucose	HbA1c	Creatinine
MP	**0**	159.1 ± 51.5	8.2 ± 1.4	0.92 ± 0.4

	3 months	175.1 ± 60.8	8.1 ± 1.4	0.92 ± 0.3
	6 months	136.3 ± 57.0	7.9 ± 1.4	1.4 ± 1.9
	p-value	**0.0912**	**0.8653**	**0.5969**
MA	**0**	155.2 ± 59.3	8.2 ± 1.7	0.85 ± 0.3
	3 months	148.2 ± 53.2	7.8 ± 1.6	0.87 ± 0.2
	6 months	127.4 ± 49.9	7.4 ± 1.5	0.95 ± 0.4
	p-value	**0.2099**	**0.3720**	**0.7814**

**Table 5– Blood parameters of patients with Diabetes Mellitus in both groups at 0 and 3 months. Data expressed as mean ± standard deviation*

Groups		**Total Cholesterol**	**HDL**	**LDL**
MP	**0**	181.0 ± 45.0	52.8 ± 15.6	105.9 ± 46.7
	3 months	166.6 ± 38.4	52.6 ± 18.7	86.9 ± 30.9
	6 months	171.1 ± 43.7	57.0± 18.7	93.6 ± 41.9
	p-value	**0.6067**	**0.7375**	**0.6071**
MA	**0**	193.8 ± 42.2	62.0 ± 29.6	96.5 ± 26.6
	3 months	185.0 ± 32.1	62.1 ± 36.8	96.7 ± 29.2
	6 months	183.6 ± 30.2	50.4 ± 19.3	94.9 ± 24.8
	p-value	**0.5797**	**0.8384**	**0.9818**

**Table 6– Blood parameters of patients with Diabetes Mellitus in both groups at 0 and 3 months. Data expressed as mean ± standard deviation*

The goal of any periodontal therapy is the regeneration of periodontal tissue and alveolar bone loss caused by PD. A fundamental principle of drug therapy is that the agent must reach the site of action in adequate concentration to be effective and to be maintained at that site for an adequate period to allow the effect to occur [22]. The current study considered a direct subgingival injection technique to deliver the MF completely into the periodontal pocket, offering the advantage of high concentration at the target site with reduced dosage, fewer applications and high patient acceptability [12]. In addition, it showed a homogeneous distribution between the genders, with a balanced average age between the groups.

Previous studies on 1% MG have shown a favorable improvement in clinical parameters, leading to a reduction in CPD and a gain in clinical attachment over a control period of 3 and 6 months [12]; [23]; [16]. In the present study, a significant reduction in CPD

was observed only in patients who received MG 1%. However, this study assessed patients with DM.

The hyperglycemic condition promoted by DM can lead to impaired host immune functions, inhibit bone formation and increase the release of pro-inflammatory cytokines such as interleukin-1β and interleukin-6 [25]. Considering the systemic conditions of the patients in this study, who were not included in previous studies, it is known that DM generates an inflammatory disorder contributing to systemic inflammation and may present a slower response to periodontal therapy when compared to patients without systemic alterations [10].

The aim of this study was to control PD and improve clinical parameters. In the first 3 months, the clinical parameters of CPD and CLI were reduced, but not significantly, while BOP, PI and GCF were significantly reduced in this period in both groups. At 6 months, there was a significant reduction in CPD only in the MP group, while BOP, PI and GCF were significantly reduced in this period in both groups. In addition, it was possible to observe that the MP group significantly reduced the number of pockets < 5mm and ≥ 5mm after the 6-month period, while the MA group only significantly reduced the number of pockets < 5mm in this same period. In the study by Rao *et al*. (2013), they evaluated MG 1% administered locally to the periodontal treatment of smokers with chronic PD and, as in this study, divided the patients into two groups. They observed that the BOP showed no difference at the beginning of the study, but later decreased significantly in the group that received MG 1%, which did not occur with the placebo group, unlike this study, which observed a significant reduction in both groups.

It is biologically plausible to associate DM with the progression of PD, since the formation of advanced glycation end products is a well-documented consequence of chronic hyperglycemia [26]. In this study, it was possible to assess that despite reducing inflammation in both groups, blood parameters were not significantly reduced, with a tendency to decrease in GJ, HbA1c, Total Cholesterol and LDL tests. Lopes *et al*. (2017) carried out a study evaluating the effect of basic periodontal treatment on glycemic control in patients with DMI and DMII. The results showed that there was no significant decrease in the HbA1c level at the end of the 6th month in the group of patients with DMII, corroborating the results of the present study.

On the other hand, 74.35% of the patients were diagnosed with insulin resistance. One of the main causes of insulin resistance is obesity, which has a negative impact on both diabetes and PD [19]. However, it was possible to observe that basic periodontal treatment was effective in controlling the inflammation promoted by PD, including those patients who had insulin resistance.

Taking this into account, it is important to understand the possible relationship between the treatment of PD and the metabolic control of DM, as the treatment of PD in these patients may cause a reduction in the soluble mediators responsible for the destruction of periodontal tissue and decrease insulin resistance in the tissue [27].

According to the American Dental Association (ADA), the prevalent rate of PD in diabetics reaches the rate of 39% in people over the age of 19. Considering that there is severe PD in people with long-term DM and poor glycemic control, it has been suggested that individuals with DM are two to three times more likely to develop periodontal disease compared to healthy patients [28].

The pathophysiology of the disease involves the host's immune defense against oral pathogens and the inflammation and destruction of local tissues. Deficiency in the clinical control of the disease causes an increase in inflammatory markers and consequently sensitizes the whole organism [29]. Bone loss in PD occurs through the action of osteoclasts; studies suggest that IL-17 can stimulate innate immune cells to produce chemokines increasing local inflammation. This cytokine has a potent osteoclastic activity negatively influencing PD [24]. When evaluating the amount of IL-17 present in the GCF, it

was observed that there was no statistically significant reduction in the period of 3 and 6 months, in both groups. Thus, it can be said that MF does not act directly on IL-17.

Ineffective plaque control by the patient ends up triggering the growth and proliferation of bacteria, giving rise to biofilm. If hygiene habits are not carried out optimally, bacterial species induce the production of endotoxins that cause gingival irritation, as well as activating inflammatory mediators [30]. Considering that PI was significantly reduced in both groups, as well as bop and GCF, there was a consequent reduction in inflammation.

It is therefore understood that the treatment of PD in these patients can lead to a reduction in inflammation and may reduce long-term insulin resistance in the tissues. New drugs adjunct to basic periodontal therapy may be effective in controlling PD in DM patients.

A limitation of the study was the adequate concentration of the gel, where previous studies on 1% GM showed a favorable improvement in clinical parameters, leading to a reduction in PCS and gain in clinical insertion in a control period of 3 and 6 months. However, in patients with diabetes mellitus, no study has been performed, therefore it is not known whether this concentration is the most appropriate.

4. CONCLUSION

According to the results obtained in this study, it can be concluded that both treatments were effective in controlling plaque and reducing inflammation and shallow pockets (< 5mm) in patients with PD and DMII over a 6-month period. However, MG 1% was more effective in reducing deeper pockets (≥ 5mm) in these patients over the same period.

Long-term randomized clinical trials are needed to demonstrate the effect of metformin gel at different gel concentrations specifically for patients with DM.

ETHICAL APPROVAL AND CONSENT

In accordance with Resolution 466/12 of the National Health Council, relating to research involving human beings, it was submitted to the Human Research Ethics Committee of the State University of Western Paraná - UNIOESTE and was approved under Opinion No. 5.333.897. The aim and nature of the study were explained to all patients or those accompanying/responsible for the patients, and they were included as study participants after agreeing and signing the free and informed consent form (FICF).

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Details of the AI usage are given below:

1.
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REFERENCES

1. Kocher T, Konig J, Borgnakke WS, Pink C, Meisel P. Periodontal complications of hyperglycemia/diabetes mellitus: Epidemiologic complexity and clinical challenge. Blackwell Munksgaard. 2018;78(1):59-97. doi: 10.1111/prd.12235.
2. Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: a review on recent drug based therapeutics. Elsevier Masson SAS. 2020. doi: 10.1016/j.biopha.2020.110708.
3. Hoogwerf BJ. Type of diabetes mellitus: Does it matter to the clinician? Cleveland Clinic Educational Foundation. 2020;87(2):100-108.
4. Almeida BB, Queiroz APG, Ferreira ACR, Dornelas GN, Coelho MMST. Periodontal conditions in patients with diabetes mellitus attended in South Fluminense reference center for diabetes and hypertension of Vassouras-RJ. Braz J Periodontol. 2015;25(4):14-26.
5. Bjerg L, Hulman A, Carstensen B, Charles M, Jorgensen ME, Witte DR. Development of Microvascular Complications and Effect of Concurrent Risk Factors in Type 1 Diabetes: A Multistate Model From an Observational Clinical Cohort Study. Diabetes Care**.** 2018;41(11):2297- 2305.
6. Kerbauy WD, Lima FRD, Perrella FA, Amorim, JBO. Glycation end products (age) and the exacerbation of periodontal disease in diabetics patients – review. R. Periodontics. 2008;18(3):20-27.
7. Sanz MS, Ceriello A, Buysschaert M, Chapple L, Demmer RT, Graziani F, et al. Scientific evidence on the links between periodontal diseases and diabetes: Consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the International Diabetes Federation and the European Federation of Periodontology. Journal of Clinical Periodontology. 2017;45(2):138–149. doi: 10.1016/j.diabres.2017.12.001.
8. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. Journal of Clinical Periodontology. 2018;45:S149–S161.
9. Zhang R, Liang Q, Kang W, Ge S. Metformin facilitates the proliferation, migration, and osteogenic differentiation of periodontal ligament stem cells in vitro. Cell Biology International. 2020;44(1):70-79.doi: 10.1002/cbin.11202.
10. Toyama G, Felipetti F, Bertoldo KP, Kottwitz LBM, Nassar CA, et al. Evaluation of different periodontal treatments modes for patients with type 2 diabetes mellitus. Journal of Public Health (Germany). 2014;22(6):529–534.
11. Nicolini AC, Grisa TA, Muniz FWMG, Rosing CK, Cavagni J. Effect of adjuvant use of metformin on periodontal treatment: a systematic review and meta-analysis. Springer Verlag. 2019;23(6):2659-2666. doi: 10.1007/s00784-018-2666-9.
12. Pradeep AR, Rao NS, Naik SB, Kumari M. Efficacy of Varying Concentrations of Subgingivally Delivered Metformin in the Treatment of Chronic Periodontitis: A Randomized Controlled Clinical Trial. Journal of Periodontology. 2013;84(2):212–220. doi: 10.1902/jop.2012.120025.
13. Pradeep AR, Nagpal K, Karvekar S, Patnaik K, Naik SB, Guruprasad CN. Platelet-Rich Fibrin With 1% Metformin for the Treatment of Intrabony Defects in Chronic Periodontitis: A Randomized Controlled Clinical Trial. Journal of Periodontology. 2015;86(6):729–737. doi: 10.1902/jop.2015.140646.
14. Pankaj D, Sahu I, Kurian IG, Pradeep AR. Comparative evaluation of subgingivally delivered 1.2% rosuvastatin and 1% metformin gel in treatment of intrabony defects in chronic periodontitis: A randomized controlled clinical trial. Journal of Periodontology, v. 89, n. 11, p. 1318–1325, 2018. doi: 10.1002/JPER.17-0434.

15. Akram Z, Vohra F, Javed F. Locally delivered metformin as adjunct to scaling and root planing in the treatment of periodontal defects: A systematic review and meta-analysis. Blackwell Munksgaard. 2018;0:1-9.
16. Pradeep AR, Patnaik K, Nagpal K, Karvekar S, Guruprasad CN, Kumaraswamy KM. Efficacy of 1% Metformin Gel in Patients With Moderate and Severe Chronic Periodontitis: A Randomized Controlled Clinical Trial. Journal of Periodontology. 2017;88(10):1023–1029.doi: 10.1902/jop.2017.150096.
17. Kurian IG, Dillep P, Ipshita S, Pradeep AR. Comparative evaluation of subgingivally-delivered 1% metformin and Aloe vera gel in the treatment of intrabony defects in chconic periodontitis patients: A randomized, controlled clinical trial. J Invest Clin Dent. 2018;9(3):e12324. Doi:10.1111/jicd.12324.
18. Zampiva MMM, Paula HNP, Cheah CW, Neto TPT, Nakamura KK, Ueda J, et al. Clinical Evaluation of Obesity In Patients with Type 2 Diabetes Mellitus after Periodontal Treatment: A Comparative Study. Journal of the International Academy of Periodontology. 2019;21(4):132-138.
19. Lopes CCP, Busato PMR, Mânica MFM, Araújo MC, Zampiva MMM, Nassar CA, et al. Effect of basic periodontal treatment on glycemic control and inflammation in patients with diabetes mellitus type 1 and type 2: controlled clinical trial. Jornal Public Health. 2017;25(4).DOI: 10.1007/s10389-017-0792-5
20. Tran DT, Gay I, Du XL, Fu Y, Bebermeyer RD, Neumann AS, et al. Assessing periodontitis in populations: A systematic review of the validity of partial-mouth examination protocols. Jornal Clinical Periodontology. 2013;40(12):1064-1071. doi: 10.1111/jcpe.12165.
21. Ribeiro ES, César AC, Souza DM, César HF, Pallos D. Plaque index in pediatric dentistry: comparative study between PASS and the O'Leary Plaque Control Record. International Jounal Of Dentistry. 2006;1(2):43-47.
22. Patil KS, Mahajani M, Choudhary SH, Aldhuwayhi SD, Thakare A, Mustafa MZ. Efficacy of 1,5% metformin gel as an adjuvant to scaling, root planning, and curettage for the treatament of infrabony defects in chronic periodontitis patients. Contemp Clin Dent. 2022;13(1):18-23. doi: 10.4103/ccd.ccd_271_20.
23. Pradeep AR, Patnaik K, Nagpal K, Karvekar S, Ramamurthy BL, Naik SB. Efficacy of locally-delivered 1% metformin gel in the treatment of intrabony defects in patients with chronic periodontitis: a randomized, controlled clinical trial. Journal of investigative and clinical dentistry. 2016;7(3):239–245. doi: 10.1111/jicd.12150.
24. Sun X, Li M, Xia L, Fang Z, Yu S, Gao J, et al.Alteration of salivary microbiome in periodontitis with or without type-2 diabetes mellitus and metformin treatment. Scientific reports. 2020;10:1-14.
25. Rao NS, Pradeep AR, Kumari M, Naik SB. Locally delivered 1% metformina gel in the treatment of smokers with chronic periodontitis: a randomized controlled clinical trial. Jounal of Periodontology. 2013;84(8):1165-71.doi: 10.1902/jop.2012.120298.
26. Nascimento GG, Leite FRM, Vestergaard P, Scheutz F, López R. Does diabetes increase the risk of periodontitis? A systematic review and meta-regression analysis of longitudinal prospective studies. Springer. 2018;55(7):653-667. doi: 10.1007/s00592-018-1120-4.
27. Bernardon P, Toyama G, Costa K, Sbardelotto B. Effects of initial periodontal treatment in moderately compensated and decompensated type 2 diabetic patients. BJMMR. 2016;13(4):1-13.
28. Mealey BL, Oates TW. Diabetes Melittus and periodontal diseases. J Periodontol. 2006;77:1289-1303.
29. Machado V, Botelho J, Lopes J, Patrão M, Alves R, Chambrone L, et al. Periodontitis impact in interleukin-6 serum levels in solid organ -transplanted patients: A systematic review and meta-analysis. Diagnostics. 2020;10(4):184.

30. Wade, WG. The oral microbiome in health and disease. Pharmacol Res. 2013;69(1):137–143

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