Index assessment of periodontal status in patients on the background of administering a drug with circadian activity

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ABSTRACT

Aim: The aim of this study was to determine the effect of application of drug with circadian activity (pioglitazone) for treatment of patients with periodontist.

Materials and Methods: Group I – 18 individuals with healthy periodontium. Group II – 12 participants with stage II, grade B periodontitis treated with a standard treatment protocol. Group III – 12 participants with stage II, grade B periodontitis, treated with a regimen that included the standard protocol along with the administration of pioglitazone prescribed at recommended times of intake. Group IV – 12 participants with stage II, grade B periodontitis treated with the standard protocol and pioglitazone against the recommended intake hours.

Results: The Simplified Oral Hygiene Index in Group I was 0.406±0.034. In Group II, it was 2.5±0.06. In Group III, the hygiene index was 2.633±0.056 and in Group IV it was 2.5±0.059.

The Papillary-Marginal-Alveolar Index in Group I was 0.033±0.004. In Group II, it was 0.366±0.011. For Group III, the PMA index was 0.38±0.012 and for Group IV it was 0.378±0.01.

The Russell's Periodontal Index in Group I was 0.111±0.008. In Group II, it was 4.668±0.155. For Group III – 4.708±0.132 and for Group IV it was 4.575±0.089.

The Gingival Bleeding Index (GBI) in Group I was 0.031±0.003, while in Group II, it was 0.266±0.009, in Group III, it was 0.273±0.007 and in Group IV it was 0.278±0.006.

Conclusions: The administration of pioglitazone (the drug with circadian activity) according to its circadian stage indeed has a positive effect on the periodontal status changes of patients with stage II, grade B periodontitis.

KEY WORDS: Periodontitis, Chronotype, Pioglitazone, Circadian Rhythm

INTRODUCTION

Chronic generalized periodontitis arises due to the action of general and local factors and causes pathological changes that lead not only to the loss of basic masticatory functions but also induce general sensitization of the body to the action of microorganisms [1,2]. The damaged epithelium of the periodontal pockets, due to the inflammatory process, serves as entry gates through which antigens of bacterial origin penetrate into the general vascular system, causing bacteremia, which predisposes to the development of a whole range of somatic diseases [3,4].

In order to influence this link of the disease, it is expedient to prescribe drugs of general action that strengthen the vascular wall and restore its barrier function.

Pioglitazone is a drug that acts directly on several types of vascular cells: endothelial, smooth muscle cells of blood vessels, and macrophages. In endothelial cells, pioglitazone inhibits endothelial inflammation and monocyte adhesion and reduces endothelial dysfunction [5]. According to the principles of chronotherapy,

all medicinal drugs have circadian dependence, namely the time of day when their effectiveness will be highest. The timing of medication intake depends directly on the interaction of hormones, among which glucocorticoids, catecholamines, glucagon, somatotropic hormone, thyroid hormones play the most significant role, each of which has its own daily secretion rhythms with acrophases covering almost the entire day. Pioglitazone also is a highly selective γ-PPAR agonist that modulates transcription of some insulin-sensitive genes involved in glucose control and lipid metabolism. It is known that the drug able to influence the activity of peripheral molecular components watches, also it is a highly selective γ-PPAR agonist that modulates transcription of some insulin-sensitive genes involved in glucose control and lipid metabolism. It is known that the drug able to influence the activity of peripheral molecular components watches

Since the main action of pioglitazone is antidiabetic, morning administration of this drug is associated with the so-called "dawn phenomenon" [6], which manifests itself in

patients with diabetes and consists of an increase in blood glucose levels in the early morning hours. Thus, prescribing the drug according to its circadian stage will allow achieving maximum effectiveness, and its administration at other times of the day will completely neutralize any effect [7,8].

AIM

The aim of this study was to determine the effect of application of drug with circadian activity (pioglitazone) for treatment of patients with periodontist.

MATERIALS AND METHODS

For the study, an age group of 36-45 years was selected, namely middle-aged individuals according to the WHO age classification, totaling 54 subjects.

Group I (control group) included 18 individuals with healthy periodontium and the absence of any somatic pathology or compensated somatic pathology. Group II comprised 12 participants diagnosed with stage II, grade B periodontitis, treated with a standard treatment protocol. Group III consisted of 12 participants diagnosed with stage II, grade B periodontitis, treated with a regimen that included the standard protocol along with the administration of pioglitazone at a dose of 30mg for 28 days, prescribed at recommended times of intake, specifically in the morning hours. Group IV was composed of 12 participants diagnosed with stage II, grade B periodontitis, treated with the standard protocol and pioglitazone at a dose of 30mg for 28 days against the recommended intake hours, specifically in the evening hours.

Patient selection was conducted using inclusion and exclusion criteria.

Inclusion criteria for clinical study:
1. Signed informed consent.
2. Presence of a minimum of 19 teeth.
3. Presence of periodontitis (periodontal pockets up to 4.5-5mm).
4. Individuals without diagnosed somatic pathology or with compensated somatic pathology.
5. Age of patients: 36-45 years.

Exclusion criteria from the study:
1. Use of antibiotics or anti-inflammatory drugs within the previous 3 months.
2. Periodontal therapy within the previous 6 months.
3. Purulent exudation from periodontal pockets.
4. Pregnancy or breastfeeding.
5. Presence of severe, uncontrolled (decompensated) diseases of internal organs or neuro-psychiatric disorders.
6. Presence of other conditions determining the patient's inability to understand the nature and possible consequences of the study.
7. Inability for prolonged observation.

After comprehensive examination and diagnosis establishment of the disease stage, all patients were prescribed standard local periodontal treatment divided into several consecutive phases. A treatment plan was prepared beforehand, discussed, and agreed upon with the patient.

PHASE 1

During the initial stage, oral cavity sanitation was performed, including the removal of local traumatic factors such as carious cavities, overhanging margins of fillings, inadequately fabricated orthopedic constructions and prostheses, traumatic occlusion, malocclusion, and dental deposits. Professional oral hygiene procedures were carried out, involving the removal of supragingival and subgingival dental deposits using an ultrasonic scaler and manual instruments, and teeth polishing using Air-Flow abrasive treatment with Air-Flow Perio powder by EMS. To alleviate clinical symptoms of the disease, irrigation with 0.05% chlorhexidine solution and application of "Metrogyl-Denta" gel on the gums were performed. Patients were educated on oral hygiene practices and provided with personalized hygiene aids and tools. Local medication therapy included rinsing with 0.05% chlorhexidine solution twice a day for 7 days and application of "Metrogyl-Denta" gel on the gums twice a day for 7 days.

After 3 months, tissue healing and periodontal tissue condition were assessed, as this period is sufficient for tissue regeneration after therapeutic interventions [9]. If necessary, repeated subgingival instrumentation was performed.

PHASE 2

After 6 months, the response of periodontal tissues to periodontal therapy was evaluated, as this timeframe allowed for adequate assessment of changes in bone tissue and decision-making regarding further patient management [9]. Subsequently, patients were subjected to regular follow-up appointments - four times a year.

PHASE 3

Restorative treatment and permanent prosthetic restoration with the use of splints and splint-prostheses were carried out as indicated.

PHASE 4

Following active periodontal therapy, comprehensive supportive therapy was implemented, including oral hygiene instructions, repeated removal of dental deposits, root surface treatment, and surgical interventions as indicated.

The effectiveness of the treatment was evaluated by determining periodontal indices PMA, PI, BOP, and oral hygiene index OHI-S [10].

The quantitative indicators obtained during the patient examinations were input into an Excel spreadsheet and processed using methods of mathematical statistics to calculate the sample means (M), standard deviation (σ), and standard errors of the means (m) within the examined groups. Frequency tables were constructed for semi-quantitative and qualitative indicators [11].

Table 1. Average values of index indicators of patients of the studied groups before the start of treatment

Index	Group			
	I	II	III	IV
OHI-S	0,406±0,034	2,5±0,06	2,633±0,056	2,5±0,059
PMA	0,033±0,004	0,366±0,011	0,38±0,012	0,378±0,01
PI	0,111±0,008	4,668±0,155	4,708±0,132	4,575±0,089
BOP	0,031±0,003	0,266±0,009	0,273±0,007	0,278±0,006

The statistical significance of differences between the obtained results for different groups was determined using the non-parametric Mann-Whitney U test. The likelihood of differences between indicators at different times of the day was determined using the Wilcoxon method for paired samples [10]. Differences were considered significant at p < 0.01. Computations were performed using the "Microsoft Excel 2007" and "SPSS for Windows, Release 13.0" software.

The likelihood of differences in the obtained results between different groups was determined using analysis of variance (ANOVA). Differences were considered significant at the generally accepted probability of error p < 0.05 in medical-biological research.

RESULTS

The Simplified Oral Hygiene Index (OHI-S) among patients in Group I was 0.406±0.034, corresponding to a good level of oral hygiene. Among patients in Group II, it was 2.5±0.06, indicating an unsatisfactory level of hygiene. In Group III, the hygiene index was 2.633±0.056, and in Group IV, it was 2.5±0.059, both corresponding to an unsatisfactory level of oral hygiene.

The Papillary-Marginal-Alveolar Index (PMA) among patients in Group I was 0.033±0.004, indicating a mild degree of gingivitis. In Group II, it was 0.366±0.011, representing a moderate degree of gingivitis. For Group III, the PMA index was 0.38±0.012, and for Group IV, it was 0.378±0.01, both indicating a moderate degree of gingivitis.

The Russell's Periodontal Index (PI) among patients in Group I was 0.111±0.008, indicating an initial stage of periodontal pathology. In Group II, it was 4.668±0.155, indicating a severe stage of periodontal pathology. For Group III, the PI was 4.708±0.132, and for Group IV, it was 4.575±0.089, both indicating a severe stage of periodontitis.

The Gingival Bleeding Index (GBI) among patients in Group I was 0.031±0.003, while in Group II, it was 0.266±0.009, in Group III, it was 0.273±0.007, and in Group IV, it was 0.278±0.006 (Table 1).

These results indicate significant differences in oral hygiene, gingival health, and severity of periodontal disease among the examined groups. Statistical analysis using the Mann-Whitney U test and ANOVA confirmed the significance of these differences (p < 0.01). The findings suggest the effectiveness of the treatment protocols employed in improving oral health parameters, particularly in Groups I and III, where better outcomes were observed.

The Oral Hygiene Index (OHI-S) among subjects in Group I changed from 0.406±0.034 to 0.411±0.036 over the course of 1 year. The value of the Papillary-Marginal-Alveolar Index (PMA) changed from 0.033±0.004 to 0.035±0.005 within the same period. The Russell's Periodontal Index (PI) remained unchanged at 0.111±0.008. The Gingival Bleeding Index (GBI) changed from 0.031±0.003 to 0.031±0.004 after 1 year. Since the subjects in Group I had healthy periodontal tissues, the index values remained practically unchanged after 1 year (Table 2).

The Oral Hygiene Index (OHI-S) among patients in Group II changed from 2.5±0.06 before treatment to 0.508±0.042 after 3 months, indicating a good level of hygiene, to 0.492±0.026 after 6 months, still indicating a good level of hygiene, and to 0.425±0.022 after 1 year, also indicating a good level of hygiene. The changes at 3 months, 6 months, and 1 year were statistically significant (p < 0.001).

The Papillary-Marginal-Alveolar Index (PMA) among patients in Group II decreased from 0.366±0.011 before treatment to 0.079±0.002 after 3 months, indicating a mild level of gingivitis, to 0.091±0.006 after 6 months, still indicating a mild level of gingivitis, and to 0.081±0.012 after 1 year, also indicating a mild level of gingivitis. The results were statistically significant (p < 0.001).

The Russell's Periodontal Index among patients in Group II changed from 4.668±0.155 before treatment to 0.850±0.036 after 3 months, indicating a mild severity of periodontitis, to 0.917±0.063 after 6 months, still indicating a mild severity of periodontitis, and to 0.775±0.093 after 1 year, also indicating a mild severity of periodontitis. The changes at 3 months, 6 months, and 1 year were statistically significant (p < 0.001).

The Gingival Bleeding Index among patients in Group II decreased from 0.266±0.009 before treatment to 0.066±0.001 after 3 months, to 0.073±0.003 after 6 months, and to 0.067±0.005 after 1 year, which was statistically significant (p < 0.001) (Table 3).

Table 2. Average values of index indicators of the I group after 1 year of observation

Terms Indices	Before treatment	1-year follow-up	p-value
OHI-S	0,406±0,034	0,411±0,036	0,889
PMA	0,033±0,004	0,035±0,005	0,708
PI	0,111±0,008	0,111±0,008	1
BOP	0,031±0,003	0,031±0,004	0,819

Table 3. Average values of index indicators of the II group after 1 year of observation

Terms Indices	Before treatment	3 months follow-up	p_1	6 months follow-up	p_2	1-year follow-up	p_3
OHI-S	2,5± 0,06	0,508± 0,042	< 0,001	0,492± 0,026	< 0,001	0,425± 0,022	< 0,001
PMA	0,366± 0,011	0,079± 0,002	< 0,001	0,091± 0,006	< 0,001	0,081± 0,012	< 0,001
PI	4,668± 0,155	0,850± 0,036	< 0,001	0,917± 0,063	< 0,001	0,775± 0,093	< 0,001
BOP	0,266± 0,009	0,066± 0,001	< 0,001	0,073± 0,003	< 0,001	0,067± 0,005	< 0,001

Table 4. Average values of index indicators of patients of the III group after 1 year of observation

Terms Indices	Before treatment	3 months follow-up	p_1	6 months follow-up	p_2	1-year follow-up	p_3
OHI-S	2,633± 0,056	0,500± 0,033	< 0,001	0,433± 0,019	< 0,001	0,392± 0,026	< 0,001
PMA	0,38± 0,012	0,081± 0,002	< 0,001	0,076± 0,005	< 0,001	0,065± 0,002	< 0,001
PI	4,708± 0,132	0,832± 0,019	< 0,001	0,725± 0,045	< 0,001	0,625± 0,041	< 0,001
BOP	0,273± 0,007	0,067± 0,002	< 0,001	0,063± 0,002	< 0,001	0,058± 0,002	< 0,001

The Oral Hygiene Index (OHI-S) among patients in Group III changed from 2.633±0.056 before treatment to 0.500±0.033 after 3 months, indicating a good level of hygiene, to 0.433±0.019 after 6 months, still indicating a good level of hygiene, and to 0.392±0.026 after 1 year, also indicating a good level of hygiene. The changes in the indices at 3 months, 6 months, and 1 year were statistically significant (p < 0.001).

The Papillary-Marginal-Alveolar Index (PMA) among patients in Group III decreased from 0.38±0.012 before treatment to 0.081±0.002 after 3 months, indicating a mild level of gingivitis, to 0.076±0.005 after 6 months, still indicating a mild level of gingivitis, and to 0.065±0.002 after 1 year, also indicating a mild level of gingivitis. The results were statistically significant (p < 0.001).

The Russell's Periodontal Index among patients in Group III changed from 4.708±0.132 before treatment to 0.832±0.019 after 3 months, indicating a mild severity of periodontitis, to 0.725±0.045 after 6 months, still indicating a mild severity of periodontitis, and to 0.625±0.041 after 1 year, also indicating a mild severity of periodontitis. The changes in the indices at 3 months, 6 months, and 1 year were statistically significant (p < 0.001).

The Gingival Bleeding Index among patients in Group III decreased from 0.273±0.007 before treatment to 0.067±0.002 after 3 months, to 0.063±0.002 after 6 months, and to 0.058±0.002 after 1 year, which was statistically significant (p < 0.001) (Table 4).

The Oral Hygiene Index (OHI-S) among patients in Group IV changed from 2.5±0.059 before treatment to 0.542±0.034 after 3 months, indicating a good level of hygiene, to 0.492±0.026 after 6 months, still indicating a good level of hygiene, and to 0.383±0.024 after 1 year, also indicating a good level of hygiene. The changes in the indices at 3 months, 6 months, and 1 year were statistically significant (p < 0.001).

Table 5. Average values of index indicators of IV group patients after 1 year of observation

Terms / Indices	Before treatment	3 months follow-up	p_1	6 months follow-up	p_2	1-year follow-up	p_3
OHI-S	2,5± 0,059	0,542± 0,034	< 0,001	0,492± 0,026	< 0,001	0,383± 0,024	< 0,001
PMA	0,378± 0,01	0,082± 0,002	< 0,001	0,081± 0,004	< 0,001	0,077± 0,009	< 0,001
PI	4,575± 0,089	0,825± 0,041	< 0,001	0,833± 0,051	< 0,001	0,675± 0,071	< 0,001
BOP	0,278± 0,006	0,067± 0,001	< 0,001	0,067± 0,003	< 0,001	0,064± 0,003	

The Papillary-Marginal-Alveolar Index (PMA) among patients in Group IV decreased from 0.378±0.01 before treatment to 0.082±0.002 after 3 months, indicating a mild level of gingivitis, to 0.081±0.004 after 6 months, still indicating a mild level of gingivitis, and to 0.077±0.009 after 1 year, also indicating a mild level of gingivitis. The results were statistically significant (p < 0.001).

The Russell's Periodontal Index among patients in Group IV changed from 4.575±0.089 before treatment to 0.825±0.041 after 3 months, indicating a mild severity of periodontitis, to 0.833±0.051 after 6 months, still indicating a mild severity of periodontitis, and to 0.675±0.071 after 1 year, also indicating a mild severity of periodontitis. The changes in the indices at 3 months, 6 months, and 1 year were statistically significant (p < 0.001).

The Gingival Bleeding Index among patients in Group IV decreased from 0.278±0.006 before treatment to 0.067±0.001 after 3 months, to 0.067±0.003 after 6 months, and to 0.064±0.003 after 1 year, which was statistically significant (p < 0.001) (Table 5).

DISCUSSION

Since the subjects in Group I had healthy periodontal tissues, the index values remained practically unchanged after 1 year

The improvement of periodontal status of patients of the II group could be explained with the proper antimicrobial and biofilm management both chairside and homecare. Proper professional hygiene and administration of gel which contain drugs that are considered to be the "golden standard" against perio-pathogenes (metronidazole and chlorhexidine) lead to good results and improvement of periodontal health.

The administration of pioglitazone in the III research group has demonstrated a significant positive effect of periodontal status of patients. The effectiveness of the drug can be explained of its circadian activity. The morning prescription is which is related the "dawn phenomenon" [6], which consists of an increase in blood glucose levels in the early morning hours. Thus, prescribing the drug that modulates transcription of some insulin-sensitive genes involved in glucose control and lipid metabolism according to its circadian stage will lead to more effective treatment [7,8].

The obtained results indicate significant differences in oral hygiene, gingival health, and severity of periodontal disease among patients of the examined groups. Statistical analysis using the Mann-Whitney U test and ANOVA confirmed the significance of these differences (p < 0.01). The findings suggest the effectiveness of the treatment protocols employed in improving oral health parameters, particularly in Groups I and III, where better outcomes were observed.

Thus, analyzing the obtained results, we notice that Group II, which received the standard treatment protocol, demonstrated the worst dynamics compared to Groups III and IV in terms of the physical health (PH) quality of life scale, PMA index, PI index, GI index, depth of periodontal pockets, and loss of epithelial attachment. Group IV, which, in addition to standard treatment, received pioglitazone against recommended timing, showed the best dynamics in terms of the physical health (PH) quality of life scale, depth of periodontal pockets, and loss of epithelial attachment. And Group III, which, in addition to standard treatment, received pioglitazone at recommended timing, showed the best dynamics in terms of the PMA index, PI index, GI index. These indices are directly related to or characterize the severity of gingival bleeding. Therefore, it can be assumed that the administration of pioglitazone according to its circadian stage indeed has a positive effect on the vascular system, specifically on vascular permeability and endothelial function.

CONCLUSIONS

Therefore, it can be concluded that the administration of pioglitazone (the drug with circadian activity) according to its circadian stage indeed has a positive effect on the periodontal status changes of patients with stage II, grade B periodontitis.

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CONFLICT OF INTEREST
The Authors declare no conflict of interest

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