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## Role of photodynamic therapy and probiotics for the treatment of periodontal disease in diabetic patients: a preliminary clinical trial

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### ABSTRACT

The aim of this preliminary *in vivo* clinical trial was to compare the effectiveness of conventional periodontal treatment with that of PhotoDinamic Therapy (PDT) and probiotic (PB) supplementation in patients with type 2 diabetes. Thirty-six diabetic patients complicated with periodontal disease were randomly divided into three groups: control group, PDT group, and PB group. Regular re-examinations were carried out on days 30, 60, and 90 after treatment. The contents of the re-examination included bleeding, periodontal pocket depth, and tooth mobility. Venous blood samples were collected on days 0, 30, and 90 of the research process. The assessed key indicators included glycated hemoglobin, glycated albumin, which accurately reflects blood glucose fluctuations over the previous 2-3 weeks, and high-sensitivity C-reactive protein, to gain insights into the body's potential inflammatory status. Sulcus bleeding index and probing depth of the periodontal pocket in the PDT and PB groups were lower than those in the control group, with a small difference between the two groups. Moreover, while the conventional periodontal treatment caused a decreasing of the three blood markers, the addition of PDT and PB did not influence these key indicators. This study suggests that integrated treatment, combining the conventional approach with PDT and PB, improves periodontal health, although it does not appear to affect glycemic control.

**Key words:** diabetes; periodontitis; photodynamic therapy; probiotics.

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The term “focal infection” indicates a theory, very popular in the late '90s, which blamed oral infections as the cause of many chronic diseases such as cancer, arthritis, atherosclerosis, and mental illnesses.<sup>1</sup> Although a 1952 editorial published in the *Journal of the American Medical Association* marked the end of this theory due to insufficient scientific evidence,<sup>2</sup> Williams and Offenbacher, in 2000, based on epidemiological studies, established a possible relationship between periodontal infections and systemic diseases, proposing the term “periodontal medicine” to define this modern, interesting approach.<sup>3</sup> Today, a relationship between periodontitis and over 50 systemic pathological conditions and diseases, including diabetes, has been evidenced.<sup>4,5</sup>

The first study about a possible connection linking periodontitis and diabetes, carried out over half a century ago, was performed on Pima Indians with type 2 diabetes, where a high incidence of periodontitis was noticed, more severe when compared to normoglycemic individuals.<sup>6</sup>

Numerous studies have confirmed that diabetes is the main risk factor for periodontitis,<sup>7-9</sup> evaluating about three times the incidence of periodontitis in diabetic patients when compared to non-diabetic ones.<sup>10</sup>

There is emerging evidence to support the existence of a two-way relationship between diabetes and periodontitis, with diabetes increasing the risk for periodontitis and periodontal inflammation negatively affecting glycemic control.<sup>11</sup> This association seems to be bidirectional, as periodontitis has been described to adversely modify glycemic control in patients with diabetes, thus contributing to the worsening of diabetic complications.

Periodontitis has been described to adversely modify glycemic control in patients with diabetes, leading to the worsening of diabetic complications, and periodontal therapy can lead to a moderate enhancement in glycemic control of diabetic patients. The potential impact of periodontal infections on diabetes can be attributed to the subsequent elevation in the levels of systemic pro-inflammatory mediators. These mediators exacerbate insulin resistance.<sup>12</sup>

An increased deposition of advanced glycation end-products (AGEs) was found in the periodontal tissues of diabetes patients, and the interactions between AGEs and their receptors, particularly common on macrophages, might lead to local immune and inflammatory response activation.<sup>13</sup>

The products of periodontal bacteria, inflammatory cytokines, and other mediators produced in the inflamed periodontal tissues may enter the circulation, contributing to upregulated systemic inflammation. This leads to impaired insulin signaling and insulin resistance, thus resulting in diabetes exacerbation.<sup>14</sup>

Periodontal treatment may improve periodontal infection management as well as general health, resulting in better control of blood glucose in diabetic patients. For this reason, given the significant impact of oral complications on quality of life, the prevention of periodontal disease and its early management appear to be essential in the care of diabetes patients.

Despite significant efforts to develop new approaches in this area, the current treatment of choice for periodontitis remains the mechanical removal of supra- and subgingival bacterial plaque, supplemented by other adjuvant therapies such as antibiotics, antiseptic substances, and host modulators.<sup>15</sup>

Photodynamic therapy (PDT) is a promising approach to fight the growing problem of antimicrobial resistance that threatens health care. PDT uses laser and/or LED light to excite a light-activated chemical agent (photosensitizer), leading to the generation of reactive oxygen species (ROS). Many PDT studies confirmed its efficacy *in vitro* and *in vivo* against bacteria, fungi, viruses, and parasites, particularly in the oral cavity<sup>16,17</sup> also in diabetic rats.<sup>18</sup>

The word “probiotics” (PBs) is derived from the Latin “*pro*”, which means “promotion”, and the Greek term “*bios*”, meaning “life”. Accordingly, PBs are considered “life-promoting” microorganisms.

The World Health Organization (WHO) defines PBs as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host”. PBs have become a useful tool for the medical community, thanks to their many benefits as well as the absence of any significant risk related to their use. Their effects are not only related to boosting the functioning of the immune system, but also to naturally helping fight harmful bacteria by supplying enough beneficial elements to maintain the body in a state of symbiosis. Unlike most traditional therapies for illnesses and diseases, this alternative treatment has no clearly described side effects, risks associated with it, or risk of overdose; these are considered practically null.<sup>19</sup>

*Streptococcus salivarius* K12 is a PB that can fight oral infections; it produces two significantly powerful proteins:

the bacteriostatic peptide salivaricin A and the bactericidal peptide salivaricin B, both referred to as “bacteriocin-like inhibitory substances”. Several studies have shown that salivaricin A and salivaricin B attack invasive bacteria by colonizing in the oral cavity.<sup>20</sup>

The aim of this preliminary *in vivo* clinical trial was to compare the effectiveness of conventional periodontal treatment to PDT and to PB assumption in type 2 diabetic patients.

## Materials and Methods

### Research subjects and grouping

In this study, patients with diabetes mellitus complicated with periodontal disease who were admitted between January 2024 and November 2024 were selected as the research subjects. The patient information was entered using the Random Number Table, and based on this, the patients were randomly divided into three groups, namely the control group, the laser group, and the PB group. Each group consisted of 12 patients from the Department of Endocrinology. Diabetic patients underwent oral screening in the Department of Stomatology, and only those of them meeting the inclusion criteria were involved in the study. The treatment course for this periodontal disease was 90 days. The gender and age of the participants are shown in Figures 1 and 2.

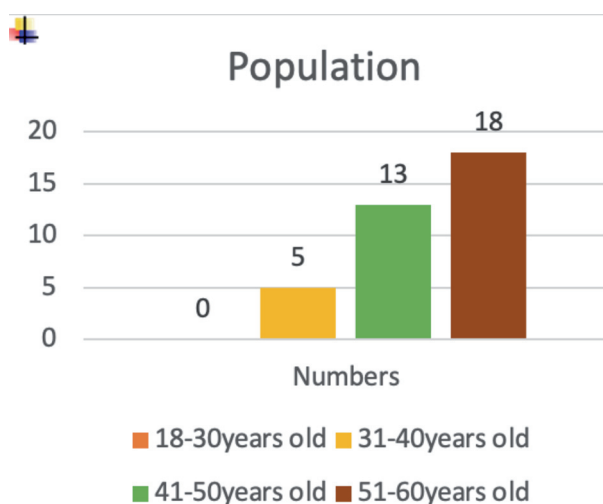


Figure 1. Patients' age distribution.

### Inclusion criteria

Inclusion criteria were: i) age between 18 and 60 years; ii) diagnosis of type 2 diabetes with fasting blood glucose  $\geq 7.0$  mmol/L; iii) confirmed diagnosis of periodontal disease; iv) no periodontal treatment within the previous 6 months; v) no smoking habit or smoke  $< 10$  cigarettes per day; vi) presence of at least 15 remaining teeth; vii) no antibiotic therapy within the last 3 months.

### Exclusion criteria

Exclusion criteria were: i) presence of systemic diseases other than diabetic complications; ii) pregnancy or lactation; iii) coagulation disorders; iv) malignant tumor diseases.

### Data collection

All patients were correctly informed about the study, and they signed a consent form to participate. They had their blood collected before the operation, and a probe was used to record periodontal-related data for subsequent analysis and research. We decided to use the Florida Probe to give all patients a constant force of 15 gm on the pockets. The Florida Probe used in this trial was the third-generation probe connected to a computer. After the probing examination, the results were directly stored

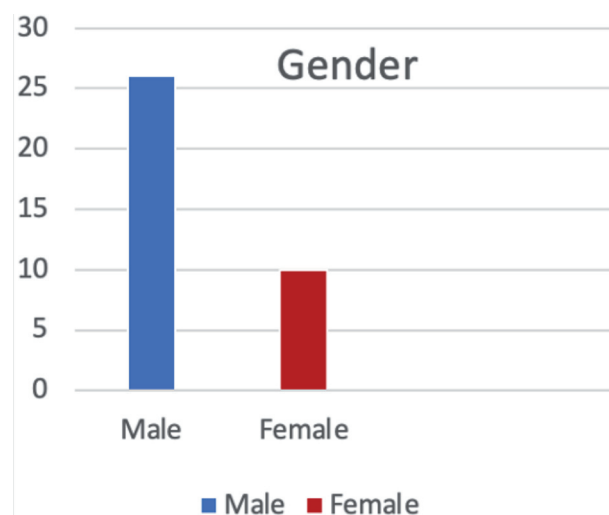


Figure 2. Patients' gender distribution.

in the inspection computer for direct comparison and analysis of various data.

The control group underwent regular basic periodontal treatment (scaling, subgingival scaling, and root planning) and then had regular reexaminations on days 30, 60, and 90.

The PDT group, after the same treatment as the control group, underwent PDT laser treatment. The syringe tip filled with 0.01% methylene blue solution (Codow, China) was gently inserted into the bottom of the periodontal pocket to fully cover the inside of the periodontal pocket, and the 635 nm laser (Smart M Pro, Lasotronix, Poland) was irradiated on the buccal and lingual sides of each tooth for 20 seconds, respectively (8 mm defocused spot, 100 mW output power, 20 J/cm<sup>2</sup> fluence).

After undergoing regular periodontal treatment, the patients in the PB group orally assumed K12 PBs (Bactoblis<sup>®</sup>, PharmExtracta, Piacenza, Italy) at a dosage of one tablet per day.

### Treatment methods

Regular periodontal treatment methods were adopted. Regular periodontal treatment generally includes supragingival scaling (dental cleaning), that is, removing dental calculus, plaque, and pigments above the gums by ultrasonic instruments; subgingival scaling, using special manual or ultrasonic instruments to remove dental calculus and plaque on the root surface below the gums; and root planning to make the root surface smooth and reduce the reattachment of plaque and dental calculus.

All patients were instructed to follow the Bass brushing

method twice a day for 3 minutes each time. When food was impacted, dental floss and interdental brushes were used. Regular re-examinations were carried out on days 30, 60, and 90 after treatment, including checking periodontal pocket depth, gingival inflammation (such as gingival color, texture, bleeding index, etc.), mobility, and other periodontal indicators. These indicators were used to evaluate the treatment effect and recovery of the periodontal tissue.

Moreover, on days 0, 30, and 90 of the research process, venous blood samples were subsequently collected. The key indicators to be detected included glycated hemoglobin, reflecting the average blood glucose status over the past 2-3 months (day 60 was therefore not indicative); glycated albumin, accurately tracking the blood glucose fluctuations in the previous 2-3 weeks; and high-sensitivity C-reactive protein, to gain insights into the potential inflammatory state of the body.

### Statistical analysis

Measurement data are presented as mean ± standard deviation (SD). For comparisons among multiple groups, analysis of variance (ANOVA) or the Kruskal-Wallis rank-sum test was applied, as appropriate.

### Results

The results of the periodontal indicator analysis are presented in Table 1, while the key indicators obtained from venous blood samples are reported in Table 2.

Table 1. Results of the periodontal indicators analysis.

	Groups	Cases	d1	d30	d60	d90
HbA1C	1	12	8.08±1.85	7.28±1.15	7.65±0.68	7.618±1.23
	2	12	8.28±1.36	6.72±0.79	6.46±0.48	7.07±0.53
	3	12	8.04±1.51	6.58±0.77	7.27±0.38	6.79±0.33
	F	-	0.03	1.5	24.065	3.283
	p	-	0.721	0.238	3.283	0.05
	GA	1	12	18.05±7.46	-	14.07±3.99
2		12	20.36±5.03	-	17.45±1.95	16.96±1.74
3		12	19.05±3.64	-	15.83±2.15	16.15±1.73
F		-	0.511	-	4.207	0.217
p		-	0.604	-	0.024	0.806
CRP		1	12	2.43±1.54	2.70±2.47	2.32±1.24
	2	12	3.02±1.74	1.95±0.86	2.97±1.23	2.61±1.20
	3	12	2.52±1.31	2.42±1.42	2.65±0.62	1.74±0.72
	F	-	0.511	0.578	1.105	1.544
	p	-	0.605	0.567	0.343	0.226

HbA1C, glycated hemoglobin; GA, glycated albumin; CRP, C-reactive protein.

**Table 2.** Results of the venous blood samples' key indicators analysis.

	Groups	Cases	d1	d30	d60	d90
Bleeding	1	12	53.92±14.49	32.50±10.84	25.08±8.06	18.42±5.81
	2	12	54.33±10.71	21.17±6.32	21.00±5.97	16.67±5.17
	3	12	49.58±9.16	20.67±5.02	19.00±6.30	15.5±4.98
	F	-	0.610	8.827	2.458	0.911
	p	-	0.550	0.001	0.101	0.412
Depth	1	12	52.85±12.38	36.5±7.96	25.83±7.13	22.83±7.48
	2	12	60.33±16.205	24.17±6.82	20.5±6.78	17.25±5.77
	3	12	55.92±7.84	25.25±6.28	21.42±5.82	18.33±4.91
	F	-	1.072	11.242	2.237	2.785
	p	-	0.354	0.000	0.123	0.076
Mobility	1	12	4.17±1.34	3.08±0.9	2.08±0.66	1.83±0.57
	2	12	4.58±1.16	3.25±0.86	2.00±0.60	1.67±0.49
	3	12	4.50±1.50	3.00±0.85	1.92±0.51	1.83±0.57
	F	-	0.323	0.255	0.232	0.367
	p	-	0.726	0.776	0.794	0.696

## Discussion

Although relatively few studies provide strong evidence supporting the role of PDT in periodontitis patients with type 2 diabetes,<sup>21</sup> several clinical studies have reported the use of PDT as an adjunct to conventional periodontal therapy, showing improvements in both clinical and biochemical outcomes, including clinical attachment level gain, reduction in probing pocket depth, and decreased bleeding on probing.<sup>22</sup>

The mechanisms by which PDT selectively kills oral bacteria, as described by Allison and Moghissi (2013), are based on the interaction among a photosensitizer, light, and reactive oxygen species. When applied to the periodontal pocket, the photosensitizer is preferentially taken up by Gram-negative bacteria owing to its hydrophilic nature, cationic charge, and low molecular weight, which facilitate its passage through the porin channels present in the outer membrane of these microorganisms. Subsequently, upon irradiation with light of an appropriate wavelength, the photosensitizer is excited to a long-lived triplet state capable of interacting with molecular oxygen.<sup>23</sup>

Many different photosensitizers, as well as different wavelengths, have been proposed to be used in periodontology. The choice depends on different factors, such as the type of lesion being treated, the desired tissue penetration depth, and the specific light source used:<sup>24</sup> methylene blue, toluidine blue, indocyanine green, malachite green, erythrosine dyes, Bengal rose, the radiochlorine group, and curcumin may be safely used with different light sources without causing any harm to the patient.<sup>25</sup>

We chose to use methylene blue in our clinical trial, as it

is a hydrophilic phenothiazinium cationic dye that may easily penetrate bacterial cell walls, inhibiting phagocytic activity.<sup>26</sup>

Moreover, it couples the ideal combination of high quantum yield to excellent chemical stability necessary for effective PDT action, and its positive charge allows it to adhere to negatively charged microbial cell surfaces, facilitating specific uptake and photosensitization.<sup>27</sup> In addition to its direct antimicrobial properties, research indicates that the activation of methylene blue *via* PDT can also trigger secondary local oxygen-dependent responses, beneficial for the healing of periodontal tissues and supporting the immune system.<sup>28</sup>

Based on phenothiazinium dyes, which show their intense absorption in the red-light region in the range of 600-680 nm,<sup>29</sup> in this trial, a laser emitting at 635 nm was used to irradiate the gingival pocket stained by methylene blue, as suggested by several authors.<sup>30,31</sup>

Recently, Doucette *et al.*, in a scoping review, stated that most of the literature indicated that PBs have a positive impact on periodontal health, as evidenced by changes in periodontal disease parameters.<sup>32</sup> In the same year, Wang *et al.*, in a randomized controlled clinical trial, demonstrated that PBs *Lactobacillus salivarius* LS97, *Lactobacillus paracasei* LC86, and *Lactobacillus acidophilus* LA85 administration to patients with chronic periodontitis reduces the abundance of pathogenic microbes associated with chronic periodontitis without causing substantial alterations to the salivary and dental plaque microbiota composition.<sup>33</sup>

The reason for this beneficial effect may be explained by considering the normal oral environment as a complex oral

ecosystem where the microbiota strives to retain a healthy dynamic state and a symbiotic relationship.<sup>34</sup> However, this state of eubiosis can be interrupted and transformed into a state of dysbiosis,<sup>35</sup> characterized by the involvement of bacterial metabolites in periodontal disease, as well as a marked difference in the metabolic profiles of the oral microbiota when compared with healthy conditions.<sup>36</sup>

Del Pilar Angarita-Díaz, in a systematic review in 2024, identified bacteria that could be key candidates for maintaining the oral microbiota of periodontal tissues owing to their association with health conditions and their antimicrobial properties. These bacteria include those of the genus *Streptococcus*, such as *S. sanguinis*, *S. oralis*, and *S. mitis*, which have been suggested as PBs for oral health.<sup>37</sup>

On the basis of these studies, we decided to use in this clinical trial the PB *S. salivarius* K12, able to reduce inflammation and induce beneficial responses, including type I and type II interferon responses.<sup>38</sup>

In this study, the sulcus bleeding index and periodontal pocket probing depth were lower in both the laser and PB groups than in the reference group, with only slight differences observed between the two treatment groups. No differences in tooth mobility were observed among the three groups. These results may suggest a potential benefit of combining these approaches with conventional treatment for periodontitis in diabetic patients, while considering that the conventional mechanical approach remains the mainstay of successful treatment.

It would also be interesting to investigate the combined use of laser therapy and PB to determine whether a synergistic effect can be achieved. This will be the focus of our future research.

As discussed before, periodontitis has been described to adversely modify glycemic control in patients with diabetes. Therefore, the second aim of this study was to evaluate whether the three different oral treatment approaches had a positive impact on systemic health. The analysis demonstrated that, while the conventional periodontal treatment positively influenced the changes of the three blood markers, no additional results were reached by the association of PDT and PB.

## Conclusions

Within the limitations of this preliminary study, including the small sample size and the short follow-up period, our findings suggest that the integrated treatment ap-

proach, combining conventional periodontal therapy with PDT and PBs, may improve periodontal health. However, no significant effect on glycemic control was observed.

**Contributions:** Meng Zhao, Carlo Fornaini: conceptualization, methodology; Huichao Wang, Yang Yang: data curation, formal analysis; Zhe Zhao, Zengyi Zhao: supervision, validation; Carlo Fornaini: writing - original draft, writing - review and editing. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

**Conflict of interest:** the authors declare they have no conflict of interest. CF is Editor-in-Chief of *Laser Therapy*.

**Ethics approval and consent to participate:** this study received ethical approval with trial registration number: SEY-KYLL-2023026 and date of registration: 2023.12.7. The study was conducted in accordance with the principles of the Declaration of Helsinki. Patients were adequately informed of the aims, methods, institutional affiliations of the researchers, the anticipated benefits and potential risks of the study, the discomfort it may entail, post-study provisions, and any other relevant aspects. The patients were informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal.

**Availability of data and materials:** no datasets were generated or analyzed during the current study.

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