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Efficacy of adjunctive photodynamic therapy on the clinical periodontal, HbA1c and advanced glycation end product levels among mild to moderate chronic periodontal disease patients with type 2 diabetes mellitus: A randomized controlled clinical trial

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ABSTRACT

Aims: To evaluate the clinical periodontal, serum glycated haemoglobin (HbA1c) and levels of advanced glycation end-products (AGEs) in the gingival crevicular fluid (GCF) among patients with periodontitis and type 2 diabetes mellitus (DM) after photodynamic therapy (PDT) as an adjunct to full-mouth disinfection (FMD).

Materials and Methods: Thirty type 2 DM patients with mild to moderate periodontitis were divided into two main groups: Group-A receiving adjunctive PDT with FMD and Group-B receiving FMD alone. Full-mouth plaque index (PI), bleeding on probing (BOP), probing depth (PD), attachment level (AL) were recorded. Serum HbA1c was assessed among all participants using a HbA1c analyser kit. Levels of AGEs in GCF were determined using enzyme-linked immunosorbent assay. Clinical periodontal and metabolic parameters were assessed at baseline, 3 months and 6 months. Differences were compared using the Friedman test within the groups for different time points. Kruskal-Wallis test with Bonferroni correction test was applied for intragroup and multiple comparisons, respectively.

Results: All the clinical periodontal parameters showed significant reduction from baseline to 3 months ($P < 0.05$) and 6 months follow-up in both the groups ($P < 0.01$). Only PD showed statistically significant difference from baseline to 3 months in Group-A ($P < 0.01$). Mean percentage of HbA1c remained constant throughout the study period in both the groups. Mean level of AGEs significantly reduced in both the groups at all time-points. Mean AGEs level reduced slightly higher in Group-A compared to Group-B at 3 months follow-up. However, this difference was not statistically significant ($P > 0.05$).

Conclusion: No additional benefit was seen in the improvement of clinical periodontal parameters and systemic (HbA1c levels) outcomes with PDT except that a minor reduction in the levels of AGEs in the GCF was observed with PDT in the short term.

1. Introduction

Type 2 diabetes mellitus (DM) is a chronic metabolic condition that is comprised of derangement of blood glucose levels due to, either in the resistance of insulin action or downgrade of insulin levels [1]. Type 2 DM has surged quadrupled in the last three decades globally and is considered as major cause of death. Although research suggests that genetic tendency plays a significant role in the individual vulnerability in the cause of type 2 DM; however dietary factors are important and primary drivers in the susceptibility of type 2 DM [2,3]. Patients with type 2 DM are susceptible to have cardiovascular complications, renal and cerebral disorders later in life. There is exhaustive research in dentistry that indicates type 2 DM is a major risk factor in the development of periodontitis [4,5].

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There are several factors that are implicated in the progression of periodontitis. These include deficiencies in the polymorphonuclear leukocyte function and alteration in the collagen metabolism [6,7]. Research also shows that bacterial pathogens such as *Porphyromonas gingivalis*, *Prevotella intermedia* and *Aggregatibacter actinomycetemcomitans* are some of the major periodontopathogens in the implication of periodontitis in type 2 DM [8]. In the chronic hyperglycemic state, several proteins undergo glycosylation that subsequently leads in the accumulation of advanced glycation end-products (AGEs) [9]. The formation of AGEs cross-link collagen that makes them less soluble with less reparative tendency of periodontal tissues [10]. Therefore, increased levels of AGEs with other altered cellular response renders the periodontal structures susceptible to periodontal breakdown [11].

Photodynamic therapy is a new adjunctive therapeutic modality that is indicated in the treatment of several oral diseases [12,13]. This technique involves the interaction of dye molecule with laser light of specific wavelength and accompanying oxygen that produces reactive oxygen species. These free radicals are highly toxic in nature and causes bacterial cell disruption [14]. Recent data reveals that PDT may be used to treat periodontal inflammation in type 2 DM with additional effects having on bleeding on probing (BOP) possibly through the reduction of several cytokines and chemokines such as vascular endothelial growth factor (VEGF) [15,16]. The outcomes of these studies suggests that PDT may be a valuable treatment modality in treating periodontitis in type 2 DM. In addition, multiple studies have shown the outcomes of glycemic levels in terms of glycated haemoglobin (HbA1c) before and after non-surgical periodontal therapy [17,18]. However, to date no study has been performed that assessed the levels of AGEs in the gingival crevicular fluid (GCF) among patients with periodontitis and type 2 DM after PDT and full-mouth disinfection (FMD).

The aim of the present 6 months clinical trial was to evaluate the clinical periodontal, serum HbA1c and levels of AGEs in the GCF among patients with periodontitis and type 2 DM with the use of PDT as an adjunct to FMD.

2. Materials and methods

2.1. Ethics and protocol

The present study protocol was approved and conducted in agreement with ethical standards established by the World Medical Association Declaration of Helsinki for research trials involving human participants. The present study was approved by the locals research ethics committee (10-18335-07). Eligible participants who fulfilled the selection criteria and agreed to the conditions of the research study were invited to sign a written informed consent. The study protocol describing the aims and objectives of the clinical study was provided to all the recruited participants.

2.2. Sample size calculation

Sample size was determined using the power calculation. It was estimated to be a total of 15 patients per group that provided 80% power for the detection of 1.0 mm of difference in the probing depth (PD) between the two groups with a standard deviation of 0.8 mm and type I error adjusted at 0.05 and type II error adjusted at 0.2.

2.3. Selection criteria

The inclusion criteria were patients with: (a) aged ≥30 years; (b) clinically diagnosed with mild to moderate periodontitis [19]; (c) self-reported type-2 DM for ≥2 years confirmed by a physician with HbA1c levels ≥6.5% [20] and; (d) patients who complied with the treatment protocol. The exclusion criteria were: (i) pregnancy and lactation; (ii) who had taken antibiotics in the previous 3 months; (iii) who had undergone periodontal therapy or any decontamination treatment in their oral cavity in the previous 6 months; (iv) former/current smokers; (v) patients with major diabetic complications and; (vi) failure to provide a signed informed consent.

2.4. Randomization and blinding

Included patients were randomized and divided into two therapeutic groups using block randomization. Successive participants (entitled by a code) after inclusion and their names entered in the envelopes to ensure that the overall sample size was equal between the treatment groups. Eight blocks (each block consisting of 5 patients) were selected. The principal investigator was informed about the randomization code, but were later revealed after analyzing the clinical data. For blinding, one assessor (SM) was responsible for rendering the therapy to all the patients, whereas one examiner (SSS) was responsible for all the clinical assessments.

2.5. Study groups

Type 2 DM patients with periodontitis were divided into two main groups: Group-A receiving adjunctive PDT with FMD and Group-B receiving FMD alone.

2.6. Full-mouth disinfection

Full-mouth disinfection was adapted from the technique described by Quirynen et al. [21]. FMD was performed using both manual curettes and ultrasonic scaler by a single blinded and expert periodontal therapist (SM) who was unaware of the study group. After FMD, patients were instructed to rinse their mouths with 0.12% chlorhexidine (CHX) gluconate rinse (Medicom DentiCare Pro-Rinse, US) and subsequent thrice irrigation of periodontal pockets with 1% CHX gel (Corsodyl Gel 1%, GSK, UK). Tongue was brushed using the same gel for 60 s. All participants were tutored oral hygiene instructions that involved rinsing with 15 ml CHX mouthrinse twice daily for 60 s and 15 days as part of their oral home care. Re-instrumentation of residual pockets were performed at successive follow-ups and all patients were re-instructed for meticulous oral hygiene instructions.

2.7. Photodynamic therapy

Single application of PDT was performed after FMD in group A [22]. A diode laser (HELBO®TheraLite – Bredent Medical, Germany) with 670 nm wavelength, power of 150 mW, fluency of 22 J/cm^2 and density of 1.1 W/cm^2 was used in this study. Methylene blue (Helbo Blue photosensitizer) with 0.005% concentration was used as a photosensitizer which was applied inside the periodontal pockets in a depth of 3 mm with the help of a blunt needle for 10 s. Laser irradiation was performed for 60 s using a flexible tip. Laser irradiation was performed at 2 points each on buccal and lingual with the tip stabilised perpendicular to the gingival tissues.

2.8. Clinical examination

Full-mouth clinical assessments were conducted at baseline, 3 months and 6 months around all teeth by a single and calibrated clinical examiner (SSS) blinded to the study groups. The study variables included plaque index (PI) and BOP that recorded dichotomous scoring to each site of the tooth as '1 – present' and '0 – absent', respectively. In addition, PD and AL were recorded at six sites (disto-lingual/palatal, mid-lingual/palatal, and mesio-lingual/palatal, mesio-buccal, mid-buccal, disto-buccal) of each tooth using a graded periodontal probe (UNC15; HuFriedy, Chicago, USA). PD was measured to the nearest millimeter from the base of the periodontal pocket to the crest of the marginal gingiva.

2.9. Serum HbA1c levels

Semi-automated HbA1c analyser (Quo-Lab® HbA1c) was used to assess the serum levels of HbA1c among all participants at chairside. All serum investigations at baseline and follow-ups were conducted by a proficient laboratory technician (kappa 0.94) who was masked to the groups.

2.10. Crevicular fluid collection

Before collection of GCF, the periodontal pockets were air dried and sites isolated by cotton rolls to prevent the contamination from saliva. Sterile paper strips were inserted for 30 s and collected twice from each participants. Blood or salivary contaminated GCF samples were wasted. Volume of each collected GCF sample was determined using a calibrated electronic gingival fluid measuring device (Periotron HAR-6000). Pooling of two samples each were performed and thereafter eluted in microcentrifuge tubes that contained 400 µl phosphate buffered saline for 1 h. All samples were then frozen at -60 °C. All crevicular fluid sampling were repeated on the same site marked initially at baseline.

2.11. Laboratory analysis of AGEs

Samples were centrifuged at 5000 x g for 15 min at 4 °C. Aliquoted samples were analyzed using enzyme-linked immunosorbent assay according to the manufacturer's recommendations to measure the levels of AGEs by a single blinded laboratory technician. The laboratory technique involves the addition of 50 µL (uL) of crevicular fluid sample into wells containing AGEs conjugated coated plate and settled for 10 min of incubation. In the next stage, 50 u L of the diluted anti-AGE antibody was combined and incubated for 60 min. Subsequently, all wells were washed using 250 u L of wash buffer. After that, Diluted Secondary Antibody-HRP Conjugate (100 u L) was added in each well and incubated for 60 min. Washing was repeated and later, 100 u L of warm Substrate Solution was added and incubated for 20 min. 100 µL of stop solution was added to each well to stop the enzyme reaction. Absorbance was read on a microplate reader using 450 nm. The total amounts of AGEs were determined as picograms per millilitre (pg/ml). Results were calculated using the standard curves created in each assay.

2.12. Statistical analyses

All clinical periodontal and metabolic parameters were analyzed per individual. Means and standard deviations (SD) were estimated for all parameters. Normality testing were computed using Shapiro-Wilk test and verified through Kolmogorov-Smirnov test. Non-parametric tests were used for each outcome as the data was not normally distributed. To compare the differences in the clinical and metabolic parameters, the Friedman test was applied within the groups for different time points. Kruskal-Wallis test with Bonferroni correction test was applied for intragroup and multiple comparisons, respectively. Inter-group means of differences were analysed using Chi-square test. P-values less than 0.05 were considered significant.

3. Results

Out of 942 patients screened and enrolled for the study, a total of 30 type-2 DM patients were recruited and randomized in to two study groups. Each group consisted of 15 patients. Fig. 1 shows a CONSORT flow diagram depicting participant selection from enrolment to analysis. The demographic details of the study groups are described in Table 1. The mean age of patients in group A and B were 51.45 years and 52.93 years, respectively. Males were higher in number in both the groups. Duration of diabetes recorded for patients in Group-A was 10.61 years and for Group-B was 11.83 years. All demographic variables were matched at baseline and showed no significant differences.

Table 2 shows clinical periodontal parameters at baseline and subsequent follow-up periods. All the clinical periodontal parameters showed significant reduction from baseline to 3 months follow-up in both the groups ($P < 0.05$). This trend was observed in the 6 months follow-up too ($P < 0.01$). Only PD showed statistically significant difference from baseline to 3 months in Group-A ($P < 0.01$). No statistically significant difference in any clinical periodontal parameter was observed when comparison was made between the groups ($P > 0.05$).

Metabolic outcomes including serum HbA1c levels and AGEs levels in GCF for both study groups are shown in Table 3. Mean percentage of HbA1c remained constant throughout the study period in both the groups. Mean level of AGEs significantly reduced in both the groups at all time-points. Mean AGEs level reduced slightly higher in Group-A compared to Group-B at 3 months follow-up. However, this difference was not statistically significant ($P > 0.05$). No statistically significant difference in any metabolic parameter was observed when comparison was made between the groups ($P > 0.05$).

4. Discussion

The present 6 months randomized clinical trial (RCT) was designed to investigate if PDT as an adjunct to FMD versus FMD alone has an effect on clinical periodontal, serum HbA1c and levels of AGEs in the GCF of chronic periodontitis patients with type 2 DM. The results of this study suggests that all clinical periodontal parameters reduced in both treatment modalities with no significant changes in the serum HbA1c levels. However, levels of AGEs slightly reduced with PDT but showed no statistical significance.

The findings of the present clinical study are in line with previous studies that compared similar therapeutic modalities [16,17,23,24]. It is note-worthy that in these studies, the clinical periodontal parameters also showed comparable outcomes with FMD alone. However, in the study by Al-Zahrani et al. [23], that compared an additional group using systemic antimicrobial doxycycline showed statistically significantly higher reduction only in the serum hbA1c levels. This could be considered an important key factor that suggests antimicrobials may be used to reduce serum HbA1c in type 2 DM patients. The present study did not used any antimicrobials and rather excluded subjects who had used antibiotics during previous months of their inclusion. The impact of antimicrobials on AGEs levels is unknown and therefore future studies could help to determine the impact of HbA1c and AGEs both in DM patients.

Interestingly, out of all clinical periodontal outcomes, only PD reduced in the PDT group. This could explain the importance of PDT in the deep periodontal pockets and how photosensitizers could be applied deep inside the periodontal space for complete eradication of harmful periodontal niche [25,26]. This is in contrast to FMD and the use of curettes that could not be instrumented in deep periodontal spaces and difficult to reach areas. In addition, the number of application of PDT sessions used were only one. The authors of the present study hypothesizes if multiple sessions of antimicrobial PDT could lead to superior periodontal outcomes compared to just single session of PDT. Further studies are needed to test this premise.

There are a plethora of studies that suggests higher levels of serum AGEs are one of the main factors for peri-implant and periodontal inflammation [27,28]. The role of increased AGEs in the crevicular fluid and serum leads to increased tissue deterioration in DM patients [9]. Future studies should focus on the therapeutic modalities that tend to reduce AGEs levels on the local level that could reflect efficacious treatment outcomes for periodontitis in diabetic subjects. In the present study, although the levels of AGEs in the GCF slightly reduced in the PDT group compared to FMD but this difference was not significant. This could be an important and a key finding that suggests

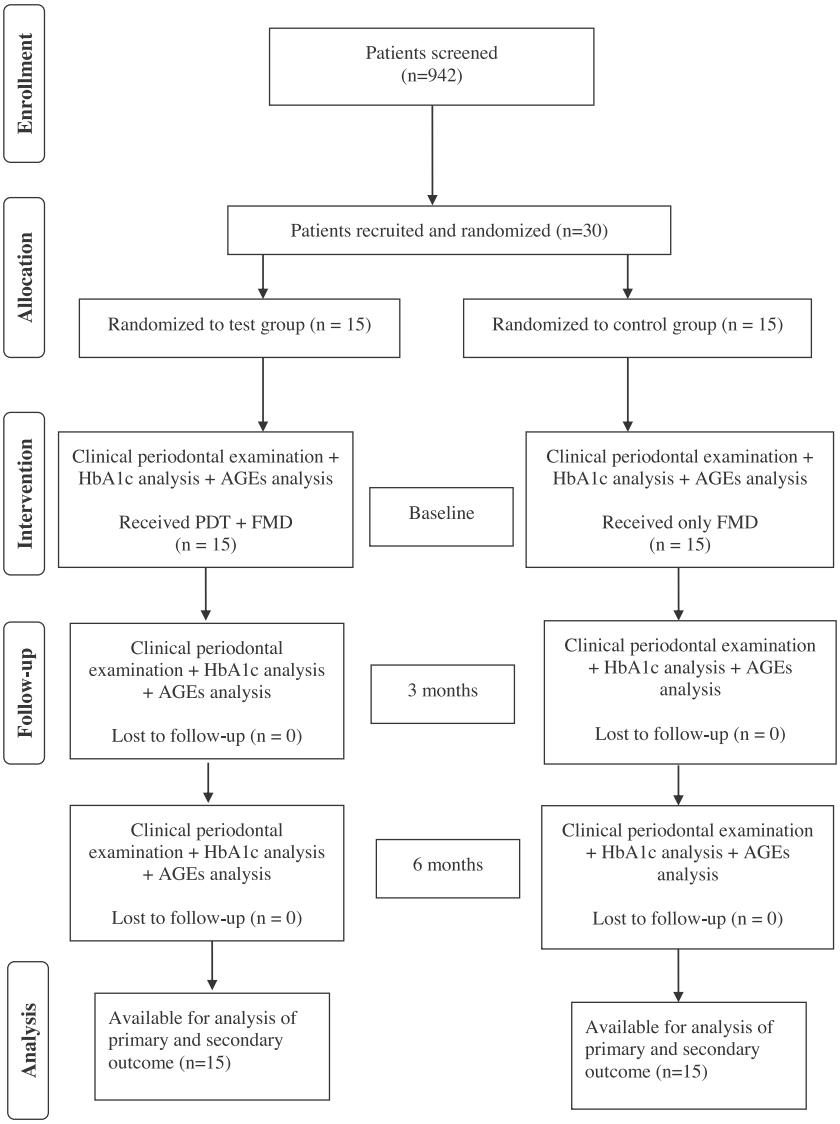

Fig. 1. CONSORT flow diagram depicting participant selection from enrolment to analysis.

Table 1
Demographics of the included patients.

Parameters	Group A (PDT + FMD)	Group B (FMD)
Number of participants (*n*)	15	15
Mean age (years)	51.45 ± 8.73	52.93 ± 7.42
Gender (M/F)	11/4	9/6
Duration of diabetes (years)	10.61 ± 2.84	11.83 ± 1.95

photobiomodulation that tends to reduce the local levels of AGEs in DM patients. This minimum reduction could be explained by the fact that PDT reduces the levels of microbial bacteria in the periodontal pockets thus further reducing the inflammatory load at the local level [29]. As higher levels of AGEs is associated with increased levels of local proinflammatory biomarkers like interleukins and tumor necrosis factor-alpha [30], this may suggest that PDT could indirectly have an impact on the levels of inflammatory cytokines. However, future clinico-laboratory studies are warranted to prove how PDT could

Table 2
Clinical periodontal parameters of the study groups at baseline and follow-ups.

Clinical parameters	Group A (PDT + FMD)			Group B (FMD)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Plaque index (0/1)	0.91 ± 0.17	0.66 ± 0.19*	0.56 ± 0.15†	0.89 ± 0.16	0.59 ± 0.18*	0.51 ± 0.19†
Bleeding on probing (0/1)	0.82 ± 0.12	0.49 ± 0.16*	0.41 ± 0.20†	0.75 ± 0.22	0.48 ± 0.25*	0.39 ± 0.29†
Mean probing depth (± SD)	3.53 ± 0.42	2.72 ± 0.38†	2.56 ± 0.41†	3.23 ± 0.61	2.94 ± 0.59*	2.69 ± 0.46†
Mean attachment level (± SD)	4.54 ± 1.11	3.93 ± 1.14*	3.41 ± 1.15†,‡	4.68 ± 1.29	4.23 ± 1.27*	3.68 ± 1.25†,‡

* *P*-value significant at < 0.05 compared with baseline.
† *P*-value significant at < 0.01 compared with baseline.
‡ *P*-value significant at < 0.05 compared with 3 months.

Table 3
Metabolic parameters of the study groups at baseline and follow-ups.

Metabolic parameters	Group A (PDT + FMD)			Group B (FMD)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Mean HbA1c in %	7.85 ± 0.21	7.24 ± 0.29	7.31 ± 0.19	7.91 ± 0.34	7.55 ± 0.38	7.49 ± 0.26
Mean AGEs in pg/ml (range)	384.73 ± 58.71	327.66 ± 69.41*	309.43 ± 78.32*	371.42 ± 65.82	338.94 ± 71.57*	318.88 ± 69.95*

* *P*-value significant at < 0.05 compared with baseline.

reduce the local levels of AGEs.

To date, a major drawback of photosensitizers in PDT is the poor uptake. The indication of amalgamating PDT with local drug delivery was undertaken in an attempt to broaden the prospect of localized therapeutic application against harmful bacteria. It is important to mention that the present study used local drug delivery for the treatment of periodontal disease. Although the possibility of antiseptics interfering with photosensitizers or laser irradiation is still unknown, however it may be speculated that the efficacy of PDT and local levels of AGEs may in turn be affected with the application of local antiseptics in the present study. Nevertheless, this interaction should be tested in future studies.

Some important limitations are described in the present study. The present study was based on a short follow-up period. Long follow-up durations may have given different outcomes in both periodontal and metabolic parameters. The present study analysed the overall mean values only on patient level and not at site level. Future studies with stratified data for both PD and AL should be reported to extrapolate outcomes at different levels. Also, the recruited participants had a mild to moderate form of periodontitis. Inclusion of severe form of periodontal disease and the changes of percentage of deep pockets could be better indicators of periodontitis severity and may help to evaluate the effect of treatment. Furthermore, the present study did not analyzed the level of proinflammatory cytokines that could help to further understand the association of AGEs and PDT outcomes at the inflammatory level. Finally, the assessment of different bacteria at baseline and concurrent follow-ups may have suggested the true efficacy of PDT in terms of microbial load in type 2 DM.

5. Conclusion

No additional benefit was seen in the improvement of clinical periodontal parameters and systemic (HbA1c levels) outcomes with PDT except that a minor reduction in the levels of AGEs in the GCF was observed with PDT in the short term.

Declaration of Competing Interest

The authors declare no conflict of interest in the present study.

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