Effects of Periodontal Treatment on Glycated Hemoglobin A Levels in Patients with Type 2 Diabetes: A Meta-Analysis of Randomized Clinical Trials

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This systematic review aimed to investigate the effects of periodontal treatment on glycated hemoglobin A (HbA1c) levels in patients with type 2 diabetes who develop periodontal disease. The search of the MEDLINE, EMBASE, CINAHL, and Cochrane Library databases was completed on April 8, 2018. The study design was based on randomized clinical trials. Scaling and root planning was performed for the test group, whereas no periodontal treatment or simple oral training was performed for the control group. The main outcome variable was the change in HbA1c levels. We used the Review Manager statistical analysis software for the quantitative analysis of selected documents. Meta-analysis was performed using the inverse variance estimation method of the fixed-effect model to estimate the effects of periodontal treatment on HbA1c levels in patients with type 2 diabetes. A total of 1,011 documents were searched using search strategies, and 10 documents were included in the meta-analysis. The meta-analysis of the selected literature showed that periodontal treatment significantly reduced the HbA1c levels in patients with type 2 diabetes (mean difference, −0.34; 95% confidence interval, −0.43 to −0.26; p < 0.001). This study aimed to investigate the effects of periodontal treatment on HbA1c levels, which can be used as a basis for the increasing management of diabetic complications. To improve the quality of life and reduce the burden of medical expenses for patients with diabetes, periodontal disease management through nonsurgical periodontal treatment, such as scaling and root planing, is necessary.

Key Words: Dental scaling, Glycated hemoglobin A, Meta-analysis, Periodontal diseases, Type 2 diabetes mellitus

Introduction

Diabetes is one of the most common chronic diseases worldwide1). As the level of physical activity decreases and the incidence of obesity increases due to lifestyle changes, the importance of diabetes consistently increases3). The prevalence of diabetes worldwide is 6.4%, and it is expected to increase up to 7.7% by 2030, resulting in a health burden at the international level1). The prevalence of diabetes in Korea is 8.23%, and it is higher than that in other countries3). Korea has become an aging society at a rapid rate and is awaiting its transition into a super-aged society; hence, the population of patients with diabetes is expected to increase rapidly3).

Type 2 diabetes, which is the most common type of diabetes, is characterized by complications of hyperglycemia and hyperlipidemia8). Periodontal diseases are the sixth most common complication of diabetes and can affect other diabetes complications such as retinopathy and coronary artery diseases5). Periodontal diseases and diabetes interact with one another6,7). In patients with periodontal diseases, the levels of systemic inflammatory mediators, such as interleukin-6, tumor necrosis factor (TNF)-α, and C-reactive proteins (CRP), which reduce insulin resistance, are elevated, which can decrease blood glucose control6,7). Periodontal diseases are infectious diseases caused by dental plaques9). In a long-term clinical study, scaling and root planing (SRP) was found to have therapeutic effects8).
The goal of nonsurgical periodontal treatment is to convert bacterial flora that cause periodontal diseases into healthy bacterial flora, to eliminate inflammatory periodontal pockets, to convert deep periodontal pockets into healthy gingival sulcus, and make the root surface appropriate for attachment to healthy epithelium and connective tissue.

Reviewing previous findings on the association between diabetes and periodontal diseases, diabetes education, diabetes treatment, and diabetes-related characteristics, such as glycated hemoglobin A (HbA1c), were associated with the prevalence of periodontal diseases, as reported in a study conducted by Jung et al. In Won and Ha’s study, the risk of impaired fasting glucose was twice as high among individuals with a community periodontal index of 2 or below than among those with an index of 3 or higher. Kim and Jang’s study on the association between metabolic syndrome and periodontal diseases in Korean adults showed that hypertension, diabetes, and dyslipidemia were associated with periodontal diseases.

Several interventional studies have hypothesized that periodontal treatment can improve metabolic control in patients with diabetes. Iwamoto et al. administered minocycline to patients with type 2 diabetes for 1 month. Their results showed that the number of microorganisms in periodontal pockets, TNF-α, glycosylated hemoglobin, and fasting insulin were significantly reduced. However, in Jones et al.’s study, no significant difference was observed between individuals who underwent periodontal treatment and the control group, 4 months after the treatment. As can be seen, study results have been inconsistent.

In a systematic review by Janket et al. that analyzed interventional studies on the effects of periodontal treatment on blood glucose control, periodontal treatment had a 0.66% effect in patients with type 2 diabetes, but the effect was not statistically significant. Although the literature included in this systematic review were interventional studies, some that did not randomize participants were also included.

Therefore, this study aimed to assess the effects of periodontal treatment on HbA1c level in patients with type 2 diabetes through a systematic review on randomized controlled trial studies.

**Materials and Methods**

1. Research design and participants

   This study is a systematic review of randomized controlled trials (RCTs) that aimed to answer the core question of “Does periodontal treatment effectively lower HbA1c levels in patients with type 2 diabetes?” Periodontal treatment was defined as SRP, and the main outcome variable was changes in the HbA1c levels.

2. Inclusion and exclusion criteria

   1) RCTs, 2) patients in the experimental group who underwent nonsurgical SRP and patients in the control group who did not undergo periodontal treatment or received simple oral health education, 3) patients diagnosed with type 2 diabetes and periodontal disease, and 4) patients aged 18 years or older were included in the study.

   1) Studies that included patients with systemic disease aside from type 2 diabetes, 2) patients who took medications known to affect periodontal tissue and treatment or those who received periodontal treatment in the last 3 months, and 3) patients who took antibiotics in the last 2 months were excluded from the study.

3. Search strategy

   Search was conducted on April 8, 2018. All literatures that have been published up to date were searched without restricting the year of publication. MEDLINE, Embase, CINAHL, and the Cochrane Library were searched. The OpenGrey (www.opengrey.eu) and domestic periodontal medicine journals were searched to find gray literatures. For search keywords, combinations of “periodontal diseases” [MeSH], “dental prophylaxis” [MeSH], “dental scaling” [MeSH], “root planing” [MeSH], and “periodontal debridement” [MeSH] joined with “diabetes mellitus” [MeSH] and “diabetes mellitus, type 2” [MeSH] by “and” were used on PubMed. To increase search sensitivity, entry terms and “periodontal non-surgical treatment OR periodontal nonsurgical therapy OR scaling root planing OR periodontal treatment OR periodontal therapy OR calculus removal” were additionally used in the search. A similar search method was used on other websites.
4. Literature selection
Two researchers independently selected literatures according to the inclusion and exclusion criteria. During the first screening, literatures were selected based on their titles and abstracts. The second screening reviewed the full text of literatures. The two researchers selected the literatures to be included in the final analysis together.

5. Statistical analysis
To review the quality of the selected literatures, the data source, study design, target participants, included factors, interventions, and results were extracted. For quantitative integration of the data, the Review Manager (RevMan) statistical analysis program (ver. 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used. Q statistics and Higgin’s I² statistic were used to assess the heterogeneity degree of the selected literatures, and the inverse variance estimation method was used depending on the heterogeneity results to perform the meta-analysis.

Results

1. Search results
Fig. 1 shows the flowchart of literature search. Using the search strategy, a total of 571 were selected from MEDLINE, 440 literatures from the Cochrane Library, Embase, and other search engines. Of the 1,011 literatures, 103 duplicates were removed. Next, 877 were removed based on their titles and abstracts. Of the remaining 31, 20 were selected following the full text review. These literatures included nine literatures that were not RCTs15-23), six in which the method of periodontal treatment was not SRP13,24-28), two in which the participants were not patients with type 2 diabetes and periodontal disease29,30), one in which the outcome variable was not HbA1c31), and two without data32,33).

2. Meta-analysis for result estimation
Table 1 summarizes the source, study design, participants, included factors, interventions, and results of the finally selected literatures4,34-43).

In a study by Kiran et al.34), the experimental group showed significant decrease in dental plaque index, decrease gingival index, reduction in periodontal pocket depth, clinical adhesion loss, and bleeding gum (p < 0.001). The experimental group showed a significant decreased in HbA1c levels (p < 0.001), while the control group showed a slight increase in HbA1c levels34).

Singh et al.35) reported that significant changes in periodontal indices were observed in experimental groups A and B following the periodontal treatment (p < 0.001). A significant decrease in the HbA1c level relative to the level in the control group was observed in the experimental
| No. | Study | Design | Participants | Inclusion criteria | Intervention | Outcomes |
|-----|-------|--------|--------------|-------------------|--------------|----------|
| 1   | Kiran et al.\(^{34}\) (2005) | RCT | 44 patients with CP and DM2; Ankara, Turkey (test: 22, control: 22) | 1) Patients with DM2 with glycated hemoglobin (HbA1c) values: 6 ~ 8% 2) Creatinine values < 1.4 mg/dl 3) Liver function tests were not up to three times the normal range 4) No major diabetic complications 5) No history of systemic antibiotic administration within the last 3 months 6) No periodontal treatment 6 months prior to the study | Test: full-mouth SRP Control: no treatment | HbA1c (at baseline, 3 months) |
| 2   | Singh et al.\(^{35}\) (2008) | RCT | 45 patients with DM2 and moderate to severe CP; Mysore, India (test (a): 15, test (b): 15, control: 15) | 1) Patients aged above 30 years of either sex, with DM2 2) Absence of any major diabetic complications 3) Moderate to advanced periodontitis (30% or more of the teeth examined having ≥ 4 mm probing depth [PD]) 4) No evidence of any systemic disease other than diabetes being a risk factor for periodontitis | Test (a): full-mouth SRP Test (b): full-mouth SRP by systemic doxycycline Control: no treatment | HbA1c (at baseline, 1, 3 months) |
| 3   | Chen et al.\(^{36}\) (2012) | RCT | 126 patients with CP and DM2; Guangzhou, China (test (a): 42, test (b): 43, control: 41) | 1) Diagnosis of DM2 for > 1 year 2) No change in their diabetic treatment plan in the previous 2 months 3) No major diabetic complication 4) Clinical diagnosis of CP according to the American Academy of Periodontology (AAP) criteria 5) ≥ 1 mm mean clinical attachment loss (CAL) 6) ≥ 16 teeth present | Test (a): full-mouth SRP at baseline and at 3 months Test (b): full-mouth SRP at baseline Control: no treatment | HbA1c (at baseline, 1.5, 3, 6 months) |
| 4   | Koromantzos et al.\(^{37}\) (2012) | RCT | 60 patients with CP and DM2; Athens, Greece (test: 30, control: 30) | 1) HbA1c levels of 7 ~ 10% (participants with DM2 are considered to be glycemic-controlled if HbA1c < 7.36) 2) ≥ 16 teeth present 3) ≥ 8 sites with PD ≥ 6 mm 4) Four sites with CAL ≥ 5 mm, distributed ≥ 2 different quadrants | Test: SRP in 2 sessions Control: supragingival cleaning | HbA1c (at baseline, 1, 3, 6 months) |
| 5   | Moeintaghavi et al.\(^{40}\) (2012) | RCT | 40 patients with mild to moderate CP and DM2; Mashhad, Iran (test: 22, control: 18) | 1) Mild to moderate periodontitis according to the criteria of the AAP 2) Diagnosis of DM2 with HbA1c value over 7% 3) No major diabetic complications 4) Blood sugar controlled with glybgemlamine and metformin, without insulin administration 5) No systemic antibiotic administration or periodontal treatment within the last six months | Test: full-mouth SRP Control: no treatment | HbA1c (at baseline, 3 months) |
| No. | Study | Design | Participants | Inclusion criteria | Intervention | Outcomes |
|-----|-------|--------|--------------|------------------|--------------|----------|
| 6   | Engebretson et al.\(^3\) (2013) | RCT | 514 patients with CP and DM2; New York, Minnesota, Alabama, and Texas, USA (test: 257, control: 257) | 1) Diagnosis of moderate CP (CAL and PD of at least > 5 mm in 2 or more quadrants of the mouth) 2) A minimum of 16 natural teeth 3) No periodontal treatment in the prior 6 months | Test: full-mouth SRP at baseline, 3 and 6 months  Control: no treatment | HbA1c (at baseline, 3, 6 months) |
| 7   | Gay et al.\(^3\) (2014) | RCT | 126 patients with CP and DM2; Houston, USA (test: 66, control: 60) | 1) Nonsmokers 2) At least 18 years old 3) Diagnosed CP with DM2 4) Hispanic origin 5) Dental treatment no less than 1 year ago 6) No systemic antibiotic therapy within 6 months of recruitment | Test: SRP at baseline and 4~6 weeks  Control: oral hygiene instructions | HbA1c (at baseline, 4 months) |
| 8   | Raman et al.\(^4\) (2014) | RCT | 32 patients with CP and DM2; Kuala Lumpur, Malaysia (test: 15, control: 17) | 1) Presence of moderate to advanced CP 2) At least 12 teeth present 3) 5 or more pockets of 5 mm or more 4) CAL of 4 mm or more in at least 2 different quadrants | Test: full-mouth SRP at baseline  Control: oral hygiene instructions | HbA1c (at baseline, 3 months) |
| 9   | Kaur et al.\(^5\) (2015) | RCT | 100 patients with CP and DM2; Rohtak, India (test: 48, control: 52) | 1) Diagnosed CP with DM2 2) Age of 45~60 years 3) Presence of ≥ 12 teeth (excluding third molars) 4) No change in medication use (oral hypoglycemics, insulin, etc.) | Test: full-mouth SRP Control: no treatment | HbA1c (at baseline, 3, 6 months) |
| 10  | Wu et al.\(^6\) (2015) | RCT | 46 patients with CP and DM2; Fujian, China (test: 23, control: 23) | 1) Diagnosis of DM2 of >1 year with no medication changes in the last 3 months 2) No nonsteroidal or anti-inflammatory drugs within the 6 months 3) No history of periodontal treatment 6 months before the study 4) Having ≥16 teeth | Test: full-mouth SRP Control: oral hygiene instructions | HbA1c (at baseline, 3, 6 months) |
| 11  | Mizuno et al.\(^7\) (2017) | RCT | 37 patients with CP and DM2; Okayama, Japan (test: 20, control: 17) | 1) Diagnosed DM2 (diagnosed at least 2 months prior to the study) 2) Diagnosis of mild to advanced CP 3) No history of periodontal treatment 6 months before the study | Test: full-mouth SRP Control: oral hygiene instructions | HbA1c (at baseline, 3, 6 months) |

RCT: randomized controlled trial, CP: chronic periodontitis, DM2: type 2 diabetes mellitus, SRP: scaling and root planning.
Chen et al.\(^{36}\) reported that significant decreases in the CRP level was observed in the two experimental groups following the periodontal treatment (p < 0.05). While the HbA1c level was significantly reduced in the second experimental group, no significant difference was observed in the HbA1c, fasting glucose, TNF-\(\alpha\), and lipid levels between the two experimental groups (p > 0.05)\(^{36}\).

Koromantzos et al.\(^{37}\) reported that a significant decrease in the HbA1c level was observed following the nonsurgical periodontal treatment in patients with type 2 diabetes and severe periodontal disease (p < 0.01). However, no significant difference was observed in the levels of hyper-sensitive CRP and matrix metalloproteinases 2 and 9\(^{37}\).

In a study by Moeintaghavi et al.\(^{4}\), a significant difference in the fasting glucose, HbA1c, total cholesterol, and cholesterol levels were observed at 3 months between the experimental and control groups (p=0.006, p=0.003, p<0.001, respectively). At 3 months, the HbA1c level was significantly reduced in the experimental group (p=0.003), while no significant change in the HbA1c level was observed in the control group\(^{4}\). Nonsurgical periodontal treatment was found to improve metabolic control in patients with diabetes\(^{4}\).

Gay et al.\(^{39}\) showed that significant changes were observed in the clinical markers of oral health between the experimental and control groups at 4 months. However, no significant difference was observed in the changes of the HbA1c level\(^{39}\).

Raman et al.\(^{40}\) showed that the HbA1c level significantly decreased in the experimental group at 3 months relative to the level during the early research period (p=0.038). Although the HbA1c level in the control group also decreased at 3 months, the decrease was significantly insignificant. No significant difference was observed in the HbA1c level between the two groups at 3 months\(^{40}\).

Kaur et al.\(^{41}\) reported that the HbA1c level in the experimental group was significantly reduced at 3 and 6 months, and the decrease was significant when compared with the control group (p < 0.05).

Wu et al.\(^{42}\) reported that no significant decrease was observed in the HbA1c level in the experimental group relative to the control group at 3 months. However, a significant decrease was observed at 6 months (p=0.00)\(^{42}\).

In a study by Mizuno et al.\(^{43}\), the balance of tissue oxidant capacity and the quality of life index significantly increased in the experimental group compared with the control group at 3 months. However, no significant difference was observed in the HbA1c level between the two groups\(^{43}\).

The results of the meta-analysis demonstrated that SNP significantly reduced the HbA1c level in patients with type 2 diabetes and periodontal disease (mean difference, −0.34; 95% confidence interval, −0.43 to −0.26; p < 0.001) (Fig. 2).

| Study or subgroup | SRP  | Control | Mean difference IV, fixed, 95% CI | Mean difference IV, fixed, 95% CI |
|-------------------|------|---------|---------------------------------|---------------------------------|
| Kiran et al.\(^{36}\), 2005 | 6.51 | 0.8 | 22 | 7.31 | 2.08 | 22 | 0.8 | −0.80 [−1.73, 0.13] |
| Singh et al.\(^{36}\), 2008 | 7.3 | 0.6 | 15 | 8.1 | 0.74 | 15 | 2.9 | −0.80 [−1.28, −0.32] |
| Chen et al.\(^{36}\), 2012 | 9.09 | 1.34 | 42 | 7.38 | 1.57 | 41 | 1.7 | −0.29 [−0.92, 0.34] |
| Koromantzos et al.\(^{43}\), 2012 | 7.15 | 0.93 | 30 | 7.46 | 0.46 | 30 | 4.8 | −0.31 [−0.6, 0.06] |
| Moeintaghavi et al.\(^{4}\), 2015 | 7.41 | 1.18 | 27 | 8.97 | 1.84 | 30 | 0.7 | −1.56 [−2.53, −0.59] |
| Gay et al.\(^{39}\), 2014 | 8.4 | 1.9 | 66 | 8.1 | 1.8 | 60 | 1.6 | 0.39 [−0.35, 0.96] |
| Raman et al.\(^{40}\), 2014 | 7.1 | 1.2 | 15 | 7.1 | 1.2 | 17 | 1.0 | 0.00 [−0.83, 0.83] |
| Kaur et al.\(^{41}\), 2015 | 7.29 | 1.61 | 48 | 8.06 | 2.72 | 52 | 0.9 | −0.77 [−1.64, 0.10] |
| Wu et al.\(^{42}\), 2015 | 7.09 | 0.12 | 23 | 7.42 | 0.18 | 23 | 85.0 | −0.33 [−0.42, −0.24] |
| Mizuno et al.\(^{43}\), 2017 | 7.5 | 1.7 | 20 | 7.7 | 1.2 | 17 | 0.8 | −0.20 [−1.14, 0.74] |

Total (95% CI) 303 295 100.0 −0.34 [−0.43, −0.26]

Heterogeneity: Chi\(^2\)=15.98, df=9 (p=0.07), I\(^2\)=44%
Test for overall effect: Z=6.27 (p<0.00001)

Fig. 2. Scaling and root planning (SRP) vs. no treatment. Glycated hemoglobin A difference between baseline and end of treatment. SD: standard deviation, IV: inverse variance estimation method, CI: confidence interval, Chi\(^2\): Q statistic, df: degree of freedom, I\(^2\): Higgin’s I\(^2\) statistic, Z: z-test.
Discussion

This meta-analysis systematically reviewed RCTs to investigate the effects of periodontal treatment on the HbA1c level in patients with type 2 diabetes and periodontal disease. The results showed that SNP reduced the HbA1c level by 0.34 in patients with type 2 diabetes and periodontal disease, which is higher than the HbA1c reduction of 0.27 observed in a previous systematic review on the effects of nonsurgical periodontal treatment on HbA1c levels published in 2015.

In the previous study, nine studies were divided into two groups based on whether the number of participants was less than 80, or greater than or equal to 80, and were separately analyzed. The HbA1c level in the studies with less than 80 participants was more greatly reduced (0.46) than that in the present study. The HbA1c level was slightly reduced (0.27) in the studies with 80 participants or more compared with that in the present study.

Following the literature search and selection processes, seven literatures included in the previous meta-analysis and three studies that have been published after this meta-analysis were included in the final quantitative integration. Although the treatment method used for one of the two experimental groups in one of the nine literatures in the previous study corresponds to the treatment method used in the present study, the resulting values of the two experimental groups were combined in the analysis conducted in the previous study, making it difficult to assess the effects of SNP only. Hence, the results of the previous meta-analysis have limited interpretation. The study by Engbretson et al. included in the previous meta-analysis combined the results from various countries, and the standard deviation for the resulting values were not clearly provided. Therefore, the study was excluded from the final analysis of the present study. Since this study more strictly applied the standard intervention in the experimental group, it could accurately measure the effects of SNP on the HbA1c level. This study is also meaningful as it included literatures published until April 8, 2018, whereas the most recently published meta-analysis only searched literatures published until 2014.

Although studies on the association between periodontal disease and systemic disease have been actively conducted, studies on the effects of periodontal treatment on the HbA1c level in patients with type 2 diabetes and periodontal disease in Korea are limited, and there are almost no RCTs investigating the same. As the prevalence of diabetes increases due to the rapid aging of Korean population, it is necessary to conduct further research to evaluate the ability of periodontal treatment to improve the HbA1c level. Therefore clinical trials on Korean patients with diabetes are required considering the fact that the patients with type 2 diabetes are relatively old, the possibility of complex chronic diseases cannot be excluded due to the increasing number of patients with average age, and the high dropout rate of patients with diabetes.

In a study that analyzed the Fourth National Health and Nutrition Survey (2009), the risk of impaired fasting glucose increased as the severity of periodontal disease increased (odds ratio, 2.18; 95% confidence interval, 1.92 ~ 2.48; p < 0.001). A study has been conducted on the association between periodontal and systemic diseases, and especially on the association between periodontal disease and diabetes. Improvements of systemic diseases through periodontal treatment based on the results of this study may be expected.

A study by Kiran et al. included 44 patients; Singh et al. 45 patients; Moeintaghavi et al. 40 patients; Raman et al., 32 patients; Wu et al. 46 patients; and that by Mizuno et al., 37 patients. Although these sample sizes were statistically calculated, they are close to the minimum number of patients required, and these studies note the small sample sizes as their limitation. A study by Chen et al. included 126 patients; Gay et al., 126 patients; Kaur et al., 100 patients. Since these studies included a larger number of patients compared with the aforementioned studies, they must have had a larger impact on the results of this meta-analysis.

The total length of the clinical trial period was 6 months in studies by Chen et al., 46', Koromantzos et al., Kaur et al., and Wu et al.; 4 months in a study by Gay et al.; and 3 months in the remaining studies. Since type 2 diabetes is a chronic disease that requires long-term care, regular periodontal treatment and long-term monitoring must be provided in patients with type 2 diabetes. Future
meta-analysis on clinical trials must include long-term studies.

Besides the 10 literatures included in the final analysis, two literatures satisfied the inclusion criteria. However, they were not included in the final analysis because their result values were not clear in the data extraction process. A study by Engebretson et al. had a relatively larger sample size of 514 patients compared with other studies, but the results had missing standard deviations. Thus, all studies could not be included in the analysis because the results remained unclear, and this was considered a limitation of this study.

Despite this, this study is considered significant as it demonstrates that periodontal treatment can improve the HbA1c level and provides a basis for the management of diabetes complications, whose incidence has been increasing.

Various studies are being conducted to evaluate the association between periodontal and systemic diseases. The need for management using nonsurgical periodontal treatments, such as SRP, to improve the quality of life and reduce the burden of medical costs is especially emphasized for diabetes.

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