

# Effect of Vitamin C as an Adjunct in Nonsurgical Periodontal Therapy in Uncontrolled Type 2 Diabetes Mellitus Patients

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## Abstract

**Objective** The main purpose of this article is to evaluate periodontal parameters of chronic periodontitis patients with uncontrolled type 2 diabetes mellitus after initial periodontal therapy plus vitamin C.

**Materials and Methods** A double-blind, placebo-controlled, clinical trial was conducted. Subjects received initial periodontal therapy plus 500 mg/day vitamin C for 2 months ( $n = 15$ ) or placebo ( $n = 16$ ). Fasting blood sugar (FBS), hemoglobin A1c (HbA1C), and plasma vitamin C level were assessed at baseline and 2 months post-treatment. Plaque Index, Sulcus Bleeding Index, Gingival Index, pocket depth, and clinical attachment level were measured at baseline, 1 month, and 2 months post-treatment.

**Results** Almost all subjects had low level of plasma vitamin C at baseline. In the test group, plasma vitamin C was significantly increased to an adequate level at the end of 2 months. After periodontal treatment, FBS and HbA1c were not significantly different compared with baseline in the test group. In the control group, FBS was significantly decreased from baseline. However, no significant difference between groups was found either in FBS or HbA1c. All periodontal parameters were significantly improved from baseline in both groups. However, no significant difference was found between groups.

**Conclusion** Supplementation of 500 mg/day vitamin C did not give an additional benefit in promoting periodontal status in periodontitis patients with uncontrolled type 2 diabetes mellitus.

## Keywords

- ▶ vitamin C
- ▶ nonsurgical periodontal therapy
- ▶ chronic periodontitis
- ▶ uncontrolled type 2 DM

## Introduction

The association between diabetes mellitus (DM) and periodontitis is generally accepted.<sup>1</sup> Several explanations underlying this association are proposed. These include an increased oxidative stress in diabetic patients,<sup>2</sup> an impaired neutrophil function, both the chemotaxis and phagocytosis<sup>3,4</sup> as well as the induction of proinflammatory cytokine and chemokine gene expression in monocytic cells.<sup>5</sup> Regarding the mucosal barrier function, thickening of gingival capillary

basement membranes caused by microangiopathies impedes oxygen diffusion and metabolic waste elimination in the gingival tissues.<sup>6</sup> In addition, the cross-linking of collagen fibers is reduced, thereby reducing the flexibility and permeability of tissue.<sup>7</sup> On the other hand, the activity of collagenase is increased.<sup>8</sup> All of these are associated with more severe periodontal tissue destruction in diabetic subjects.

Vitamin C is one of the essential micronutrients for humans. It acts as an antioxidant and can promote wound healing.<sup>9</sup> In subjects with DM, plasma vitamin C was significantly

lower compared with healthy individuals.<sup>10</sup> Low plasma vitamin C is due to an increase in clearance in patients with diabetic nephropathy.<sup>11</sup> The elevated plasma free radicals caused by hyperglycemia also reduce antioxidants including vitamin C.<sup>12</sup>

Due to its antioxidation and wound healing promotion, the effect of vitamin C supplementation in DM patients with periodontitis should be of interest. However, few studies were found.<sup>13</sup> Gokhale et al<sup>13</sup> investigated the effect of vitamin C supplementation plus nonsurgical periodontal treatment on chronic periodontitis patients with freshly diagnosed type 2 DM. They reported a significant reduction in sulcus bleeding after dietary supplementation of 450 mg vitamin C. Although the beneficial effect of vitamin C was demonstrated, the follow-up period was only 2 weeks.<sup>13</sup> Thus, we aimed to evaluate, for 2 months, the effect of vitamin C as an adjunct in nonsurgical periodontal therapy in chronic periodontitis patients with uncontrolled type 2 DM.

## Materials and Methods

This study was a double-blind, placebo-controlled clinical trial. Ethical approval was obtained from the Faculty of Dentistry/Faculty of Pharmacy, Mahidol University, Institutional Review Board (COA.No.MU-DT/PY-IRB 2016/061.0711) and Faculty of Medicine, Burapha University (No.001/2560). The study was registered in clinicaltrials.gov (NCT03269799).

### Study Population

Type 2 DM subjects were recruited from Internal Medicine Clinic, Burapha University Hospital, Chonburi. Eligible subjects were informed and those who were willing to participate were referred to Dental Clinic, Burapha University Hospital for a comprehensive periodontal examination. Subjects who fulfilled the criteria were provided with a written informed consent. Before the experiment, oral hygiene instruction and motivation were given until Plaque Index<sup>14</sup> was  $\leq 0.5$ .

### Inclusion Criteria

Uncontrolled type 2 DM subjects were recruited (fasting blood sugar [FBS] of  $> 150$  mg/dL and hemoglobin A1c [HbA1c] of  $> 7\%$ ).<sup>15</sup> Inclusion criteria for periodontitis were moderate chronic periodontitis (clinical attachment level (CAL) of  $\geq 3$  mm) according to the previous report<sup>16</sup> but slightly modified by selecting tooth with pocket depth (PD) of  $\geq 5$  mm in at least one tooth.

### Exclusion Criteria

Subjects who affected with DM complications, receiving insulin injection<sup>17</sup> or medications that could interact with vitamin C<sup>18</sup> or suffered from any conditions that affected with vitamin C excretion, pregnancy, smoking,<sup>19</sup> receiving periodontal treatment or other vitamin supplementation in the previous 6 months.

### Sample Size Calculation and Random Allocation

Sample size was calculated based on Sulcus Bleeding Index.<sup>13</sup> At a two-sided type I error of 0.05, 80% power of detection, a sample of 12 subjects was required. To compensate for 20%

dropouts, at least 15 subjects were recruited for each group. Subjects were stratified by age and gender and randomly allocated by one researcher (SR) to the test (500 mg/day vitamin C) or control (placebo) group.

### Baseline Examination

The study design was shown in (►Fig. 1). Blood samples were collected for the determination of plasma vitamin C, FBS, and HbA1c. Subjects saw medical doctors for DM follow-up. Periodontal parameters were recorded by a blinded and calibrated examiner (PK). Plaque Index, Gingival Index (GI),<sup>20</sup> Sulcus Bleeding Index,<sup>21</sup> PD, and CAL were recorded using a UNC-15 probe (Hu-Friedy, Illinois, United States) from one tooth with the deepest PD and without furcation involvement, periapical lesion, or endodontic involvement. Then, subjects received full mouth scaling and root planning and were prescribed 500 mg/day vitamin C (Government Pharmaceutical Organization, Thailand) or size- and color-identical placebo (Department of Pharmaceutical Industry, Faculty of Pharmacy, Mahidol University, Thailand). Vitamin C or placebo was kept in the concealed plastic bags and was prescribed for a duration of 30 days at a time.

### One-Month Evaluation

Periodontal parameters and any adverse effects were recorded. Residual vitamin C or placebo tablets were counted for an indirect evaluation of patients' compliance. Vitamin C or placebo was prescribed for another 1 month.

### Two-Month Evaluation

Blood sample was collected. Periodontal parameters were recorded. Residual vitamin C or placebo tablets were counted. Adverse effects, if any, were recorded.

### Statistical Analysis

Data were analyzed using SPSS for Windows (version 23). Within and between group comparisons of plasma vitamin C, FBS and HbA1c were done using Wilcoxon signed rank test and Mann-Whitney U test, respectively. Within and between group, comparisons of periodontal parameters were done using Friedman test and Mann-Whitney U test, respectively. For multiple intragroup comparison, Bonferroni post-hoc test was performed. Significant level was set at  $p \leq 0.05$  for all tests.

## Results

Thirty-one subjects were participated. None of them was withdrawn from the study. Subject characteristics at baseline were shown in (►Table 1). No statistical significance in subject characteristics was found between groups.

### Level of Plasma Vitamin C, Fasting Blood Sugar, and Hemoglobin A1c

At baseline, 73 and 68% of subjects in the test and control group, respectively, had deficient to low plasma vitamin C level ( $< 23$   $\mu\text{mol/L}$  according to Jacob and Sotoudeh<sup>22</sup>). No significant difference in plasma vitamin C, FBS, and HbA1c was found between groups (►Table 2).

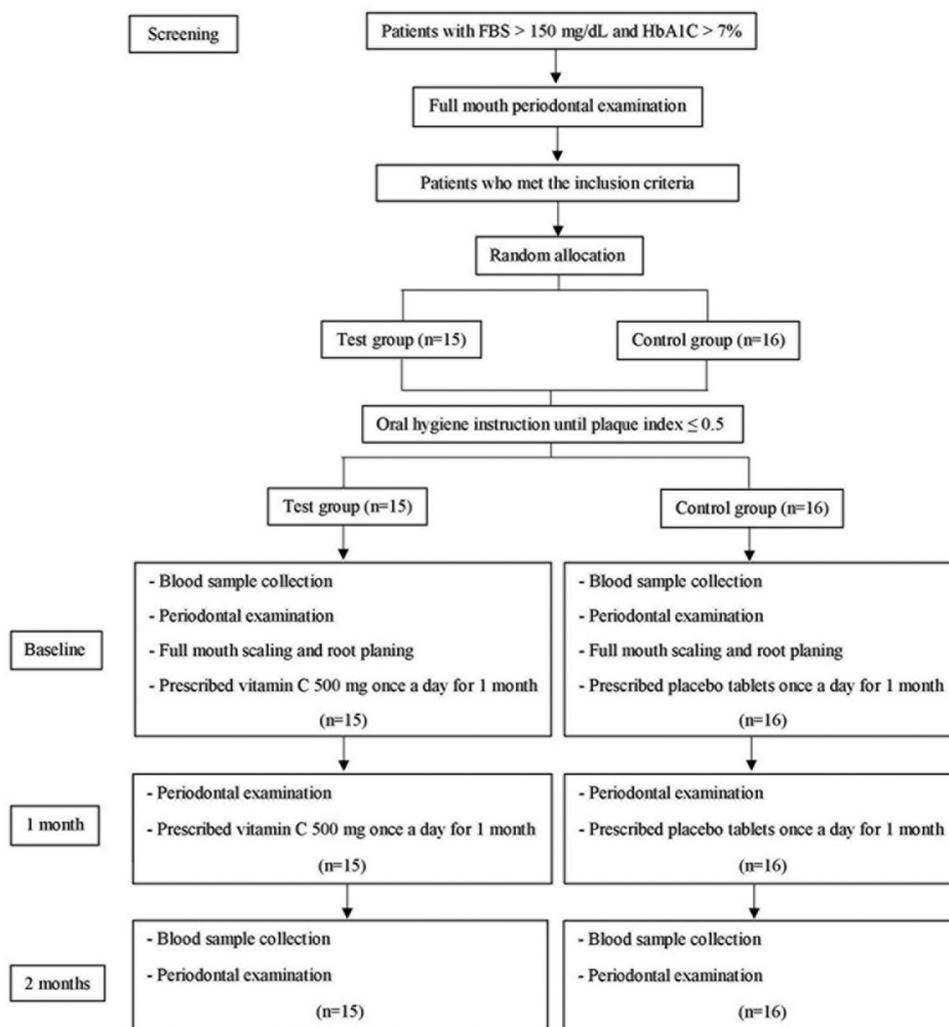


Fig. 1 Study design.

Table 1 Subject characteristics at baseline

	Test (n = 15)	Control (n = 16)
Age (years)	59.87 ± 11.3	57.94 ± 14.0
No. (%) of female	11 (73.3)	11 (68.8)
No. (%) of male	4 (26.7)	5 (31.3)
Duration of type 2 diabetes mellitus (year)	7.86 ± 4.16	7.64 ± 4.42

At 2-month evaluation, plasma vitamin C in the test group was significantly elevated compared with baseline and the control group. In the test group, FBS and HbA1c were not significantly different compared with baseline. In the control group, FBS was significantly decreased from baseline. However, no significant difference between groups was found either in FBS or HbA1c.

#### Periodontal Parameters

At baseline, no any parameter was significantly different between groups (► Table 3). Throughout the study, subjects could control their oral hygiene status. Sulcus bleeding

index, GI, PD, and CAL were significantly different compared with baseline, indicating periodontal improvement in both groups. However, no significant difference in all periodontal parameters was found between groups at any time interval.

#### Adverse Effect and Compliance

No adverse effect was reported. Both groups complied to the course of vitamin C or placebo.

#### Discussion

Periodontitis is an inflammatory condition that enhances the generation of reactive oxygen species.<sup>23</sup> However, hyperglycemia increases free radical concentration, leading to the reduction in pancreatic  $\beta$  cell function and induction of insulin resistance and poor glycemic control.<sup>12</sup> Vitamin C, as an antioxidant, can decrease oxidative stress.<sup>24</sup> Along with its wound healing promotion effect,<sup>24,25</sup> we questioned that vitamin C supplementation plus nonsurgical periodontal therapy could improve periodontal parameters in subjects with uncontrolled type 2 DM.

**Table 2** Level of plasma vitamin C, fasting blood sugar, and hemoglobin A1c

		Test	Control	p-Value
Plasma vitamin C (µmol/L)	Baseline	18.54 ± 11.00	20.01 ± 18.84	0.599
	2 months	27.77 ± 15.55	17.40 ± 14.90	0.049 <sup>b</sup>
	Difference between baseline–2 months	9.23 ± 14.57	- 2.62 ± 9.31	0.017 <sup>b</sup>
	p-Value	0.036 <sup>a</sup>	0.179	
FBS (mg/dL)	Baseline	168.53 ± 16.62	179 ± 49.04	0.654
	2 months	165.87 ± 51.76	170.13 ± 59.76	0.861
	Difference between baseline–2 months	- 2.67 ± 52.81	- 8.88 ± 36.08	0.953
	p-Value	0.280	0.046 <sup>a</sup>	
HbA1c (%)	Baseline	7.53 ± 0.79	8.39 ± 1.50	0.202
	2 months	7.27 ± 0.88	7.98 ± 1.85	0.423
	Difference between baseline–2 months	- 0.26 ± 0.80	- 0.41 ± 0.89	0.599
	p-Value	0.279	0.059	

Abbreviations: FBS, fasting blood sugar; HbA1c, hemoglobin A1c.

Statistical significance at  $p < 0.05$ .

<sup>a</sup>Wilcoxon signed rank test.

<sup>b</sup>Mann–Whitney U test.

**Table 3** Periodontal parameters

		Test			Control			p-Value
Plaque Index	Baseline	0.37 ± 0.14	} <sup>a</sup>	} <sup>a</sup>	0.33 ± 0.11	} <sup>a</sup>	} <sup>a</sup>	0.358
	1 month	0.24 ± 0.11			0.26 ± 0.12			0.770
	2 months	0.15 ± 0.07			0.16 ± 0.08			0.770
	p-Value	<0.001 <sup>b</sup>			<0.001 <sup>b</sup>			
Sulcus Bleeding Index	Baseline	3.22 ± 0.46	} <sup>a</sup>	} <sup>a</sup>	3.00 ± 0.45	} <sup>a</sup>	} <sup>a</sup>	0.188
	1 month	1.9 ± 0.59			2.00 ± 0.57			0.861
	2 months	0.57 ± 0.24			0.59 ± 0.24			0.830
	p-Value	<0.001 <sup>b</sup>			<0.001 <sup>b</sup>			
Gingival Index	Baseline	1.04 ± 0.34	} <sup>a</sup>	} <sup>a</sup>	1.15 ± 0.32	} <sup>a</sup>	} <sup>a</sup>	0.401
	1 month	0.60 ± 0.16			0.66 ± 0.21			0.520
	2 months	0.42 ± 0.09			0.45 ± 0.10			0.572
	p-Value	<0.001 <sup>b</sup>			<0.001 <sup>b</sup>			
Pocket depth (mm)	Baseline	5.2 ± 0.41	} <sup>a</sup>	} <sup>a</sup>	5.63 ± 1.09	} <sup>a</sup>	} <sup>a</sup>	0.358
	1 month	3.25 ± 1.09			3.73 ± 1.09			0.151
	2 months	3.25 ± 0.96			3.6 ± 0.90			0.232
	p-Value	<0.001 <sup>b</sup>			<0.001 <sup>b</sup>			
Clinical attachment level (mm)	Baseline	5.31 ± 0.72	} <sup>a</sup>	} <sup>a</sup>	6.05 ± 1.73	} <sup>a</sup>	} <sup>a</sup>	0.247
	1 month	3.66 ± 1.51			4.13 ± 1.73			0.401
	2 months	3.78 ± 1.17			3.93 ± 1.41			0.892
	p-Value	0.001 <sup>b</sup>			0.001 <sup>b</sup>			

Statistical significance at  $p < 0.05$ .

<sup>a</sup>Bonferroni post-hoc test.

<sup>b</sup>Friedman test.

In this study, vitamin C at a dose of 500 mg daily was chosen according to the previous studies.<sup>13,26</sup> Gokhale et al<sup>13</sup> reported that scaling and root planning plus 450 mg/day of vitamin C in chronic periodontitis subjects with freshly diagnosed type 2 DM resulted in a significant sulcus bleeding reduction. Levine et al<sup>26</sup> demonstrated that after single dose of 500 mg and higher, the bioavailability of vitamin C declined and excretion increased. At 1,000 mg of vitamin C, oxalate and urate excretion were elevated.<sup>26</sup>

After initial periodontal treatment, periodontal health was improved without significant difference between groups. Our result was inconsistent to the previous study<sup>13</sup> and probably due to the difference in subject characteristics. Subjects in the study of Gokhale et al<sup>13</sup> were freshly diagnosed type 2 DM, while those in our study were uncontrolled type 2 DM. It is known that severity and progression of periodontal disease are increased in uncontrolled DM patients.<sup>27</sup> Moreover, some subjects in our study had an adequate plasma vitamin C level at baseline (data not shown). Thus, vitamin C supplementation to adequately nourished people might not affect with periodontal integrity.<sup>22,28</sup> These two factors might mask the beneficial effect of vitamin C.

Periodontitis and DM have a bidirectional relationship.<sup>29,30</sup> However, the effect of periodontal therapy on glycemic control was still in doubt<sup>29,31</sup> and was not the objective of the present study. It was shown that nonsurgical periodontal therapy in diabetic patients could reduce HbA1c by ~0.4%.<sup>29</sup> In this study, HbA1c was reduced after initial periodontal treatment, but the reduction was not significant in both groups. Our result was supported by Mizuno et al<sup>31</sup> that nonsurgical periodontal treatment improved systemic oxidative stress balance and quality of life, but did not significantly decrease HbA1c levels at 3 months follow-up in type 2 DM patients.<sup>31</sup> Indeed, level of glycemic control depends on factors other than periodontal treatment, for example, behavior, sugar and food intake, exercise, stress, use of hypoglycemic medication, duration of treatment, and level of education.<sup>32,33</sup> Another explanation is the study period of 2 months was inadequate to observe the change in glycemic control. Although the reduction in HbA1c was not statistically significant (0.26% in the test group and 0.41% in the control group), it could have a clinical impact since it could reduce the risk of microvascular complication and mortality rate by more than 10% at the population level.<sup>34</sup> Thus, we agreed with Casanova et al<sup>29</sup> that periodontal treatment should be a part of the overall management of DM.<sup>29</sup>

Supplementation of 500 mg/day vitamin C for 2 months did not affect FBS and HbA1c in this study. This finding might be explained by the study of Yue et al<sup>35</sup> that both plasma ascorbic acid and its urinary excretion correlated inversely with glycosylated hemoglobin level. In addition, abnormalities of vitamin C metabolism and its higher turnover were found in diabetics patients over the normal volunteers.<sup>36</sup>

In conclusion, supplementation of 500 mg/day vitamin C plus initial periodontal therapy in periodontitis subjects with uncontrolled type 2 DM did not give an additional benefit in promoting periodontal status.

## Conflict of Interest

None declared.

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