Nifedipine Intake Increases the Risk for Periodontal Destruction in Subjects With Type 2 Diabetes Mellitus

Xiao Li,*† Qingxian Luan,* Xingyu Wang,‡ Yueqin Sha,* Lu He,* Caifang Cao,* and Lijian Jin†

Background: This study investigated the possible association of nifedipine (NIF) intake and diabetes mellitus (DM) with periodontal destruction.

Methods: A group of Chinese subjects (N = 1,083, age: 63 ± 8.7 years) were screened. Three hundred fifty-eight non-smokers with hypertension were selected for the study and were grouped based on DM status as non-DM and DM groups, DM(–) and DM(+) respectively. NIF(+) and NIF(–) indicated NIF intake or not. The groups were further divided: NIF(–)/DM(–) (n = 135); NIF(+)/DM(–) (n = 108); NIF(–)/DM(+) (n = 64); and NIF(+)/DM(+) (n = 51). The periodontal conditions in anterior teeth were assessed using plaque index, sulcus bleeding index, clinical attachment loss (AL), probing depth (PD), and the number of missing teeth.

Results: Using analysis of covariance, NIF intake was associated with mean PD and extent of PD ≥4 mm in the non-DM and DM groups. The subjects in the NIF(+)/DM(+) subgroup showed greater mean AL and percentage of sites with AL ≥5 mm and AL ≥7 mm than those in NIF(–)/DM(+) subgroup, whereas no significant difference existed between subjects in NIF(–)/DM(–) and NIF(+)/DM(–) subgroups. The NIF(+)/DM(+) subgroup exhibited a greater percentage of sites with AL ≥5 mm (35.5%) compared to the other three subgroups (24.7% for NIF[–]/DM[–], $P = 0.004$; 25.0% for NIF[+]/DM[–], $P = 0.007$; and 25.2% for NIF[–]/DM[+], $P = 0.016$). Logistic regression analysis showed that the NIF(+)/DM(+) subgroup had a significantly higher risk for having >10% of sites with AL ≥5 mm compared to the NIF(–)/DM(–) subgroup (odds ratio [OR] = 2.9; 95% confidence interval [CI]: 1.2 to 7.4; $P = 0.022$), the NIF(+)/DM(–) subgroup (OR = 3.1; 95% CI: 1.2 to 8.1; $P = 0.020$), and the NIF(–)/DM(+) subgroup (OR = 5.1; CI: 1.8 to 14.3; $P = 0.002$).

Conclusion: NIF intake may increase the risk for periodontal destruction in patients with type 2 DM. *J Periodontol 2008; 79:2054-2059.*

KEY WORDS

Diabetes; epidemiology; periodontitis; risk factors.

* Department of Periodontology, Peking University School and Hospital of Stomatology, Beijing, China.
† Department of Periodontology, Faculty of Dentistry, The University of Hong Kong, Hong Kong, China.
‡ Beijing Hypertension Prevention and Management Institute, Beijing, China.

Nifedipine (NIF) is a calcium channel blocker (CCB) that is mainly prescribed for controlling hypertension. Studies[1,2] reported that NIF intake was associated with gingival overgrowth, with the prevalence ranging from 6.3% to 50.8%. Although the mechanism of NIF-related gingival overgrowth remains unclear, NIF may modulate cell cycles in gingival fibroblasts[3] and disrupt the balance between the proliferation and apoptosis of fibroblasts through the blockage of L-type Ca^{2+} channels.[4] NIF may also affect the distributions of macrophage subpopulations[5] and induce the development of effector T cells as well as predominant T helper 1 activity.[6] The altered host response of periodontal tissue increased the production of chemokines and cytokines, which controlled wound healing and connective tissue turnover.[7] Related studies showed that NIF may affect bone physiology and metabolism,[8,9] inducing alveolar bone destruction and periodontal destruction.[10,11]

Type 2 diabetes mellitus (DM) is a systemic disease of the innate immune system,[12] and patients with DM are prone to severe periodontitis,[13,14] which is considered its sixth complication.[15] Because there was no significant difference in the subgingival biofilm between periodontitis patients with or without DM,[16,17] it was hypothesized that alterations in the host response (i.e., exaggerated host immune responses) induced by DM may play a crucial role in periodontal pathogenesis:[18,19]

doi: 10.1902/jop.2008.080033

glucose-mediated advanced glycation end products can increase the production of proinflammatory cytokines and mediators, which could contribute to periodontal destruction.[20,21]

Little information is available on the possible association of NIF intake and DM with periodontal conditions. This cross-sectional study was performed to investigate whether NIF intake and DM are related to periodontal destruction.

MATERIALS AND METHODS

Selection of Subjects

One thousand eighty-three subjects were recruited from a cohort of Chinese adults that was under regular care at the Beijing Hypertension Prevention and Management Institute. The participants resided in four communities at Shi Jing Shan District, Beijing. The study was approved by the Peking University Ethics Committee, and written informed consent was obtained from all subjects. This investigation was conducted from May to September 2005.

Three hundred fifty-eight subjects were selected for the study with the following inclusion criteria: essential hypertension, non-smoker, at least two permanent anterior teeth, no use of a drug that could affect gingiva (e.g., phenytoin and cyclosporin A), and no periodontal therapy within 6 months. Exclusion criteria were taking other CCBs, taking NIF for <6 months, or type 1 DM. Type 2 DM was confirmed from the medical history updated by the Beijing Hypertension Prevention and Management Institute with the World Health Organization diagnostic criteria.[22] Based upon DM condition, the subjects were divided into two groups: non-DM group and DM group, DM(−) and DM(+), respectively. Depending on NIF intake, NIF(+) and NIF(−) indicated NIF intake or not, and the two groups were divided into four subgroups: NIF(−)/DM(−) (n = 135); NIF(+)/DM(−) (n = 108); NIF(−)/DM(+) (n = 64); and NIF(+)/DM(+) (n = 51).

Interview by Questionnaire

Demographic characteristics, systemic diseases, medication details, and the history of dental treatment were recorded for each subject through an extensive questionnaire and interview. To confirm the usage of the medication, the patients were asked to show evidence of their daily use, i.e., package inserts. The body mass index (BMI) was calculated. The levels of education were defined according to the years of education: low (≤6 years), middle (7 to 12 years), and high (≥13 years).

Blood Assay

Ten milliliters of fasting whole blood was collected from each subject. Blood glucose and high-sensitivity C-reactive protein (hs-CRP) levels were assessed by an automatic analyzer.[§]

Periodontal Examination

The periodontal examinations were performed by a single examiner who was masked to the patients' medical history and medication information. The periodontal examination was confined to the 12 anterior teeth and included plaque index,[23] sulcus bleeding index (SBI),[24] attachment loss (AL), probing depth (PD), and the number of missing anterior teeth.

Statistical Analysis

The clinical parameters were calculated for each subject. The normality of different variables was tested before analysis. Parametric or non-parametric analysis was used as appropriate. The differences in the periodontal conditions were analyzed with analysis of covariance (ANCOVA), adjusting other variables, i.e., age, gender, education level, BMI, antibiotics intake, plaque index, and SBI, and pairwise comparisons were made using the Tukey method. Adjusting the same potential confounding variables in ANCOVA, logistic regression analysis was used to analyze the risk for having >10% of sites with AL ≥5 mm among the four subgroups. A P value <0.05 was considered statistically significant. All statistical analyses were performed using a software program.[‖]

RESULTS

Among the four subgroups, there was no significant difference in age, gender, education level, BMI, antibiotic intake within 3 months, bleeding on brushing, hs-CRP serum level, or plaque index (Table 1). In NIF(−)/DM(+) and NIF(+)/DM(+) subgroups, the median fasting blood sugar was 7.9 mmol/l (range: 4.8 to 18.9 mmol/l) and 6.8 mmol/l (range: 4.2 to 18.9 mmol/l), respectively, which were significantly higher than in the other two subgroups (P<0.001). The difference in the control of blood glucose between NIF(−)/DM(+) and NIF(+)/DM(+) subgroups, as well as the daily dosage and duration of NIF intake between NIF(+)/DM(−) and NIF(+)/DM(+) subgroups, did not reach statistical significance.

With regard to the periodontal conditions in the non-DM group with or without NIF intake, after adjusting for other variables, i.e., age, gender, education level, BMI, antibiotics intake, plaque index, and SBI, ANCOVA analysis showed that only mean PD and the percentage of sites with PD ≥4 mm were statistically different (P<0.05), with values of 2.3 mm (95% confidence interval [CI]: 2.2 to 2.4 mm) versus 2.5 mm (2.4 to 2.6 mm) and 10.1% (95% CI: 7.4% to 12.9%) versus 15.1% (12.0% to 18.2%), respectively. There was no significant difference in the number of missing anterior teeth, the mean AL, and the extent of the various severities of AL (Table 2).

§ 7060, Hitachi, Tokyo, Japan.
‖ SPSS 14.0 for Windows, SPSS, Chicago, IL.

Table 1.

Demographic and Medical Data of Study Subjects

Variable	Non-DM Group		DM Group	
	NIF(–)/DM(–) (n = 135)	NIF(+)/DM(–) (n = 108)	NIF(–)/DM(+) (n = 64)	NIF(+)/DM(+) (n = 51)
Median age (years [range])	65.8 (45.3 to 85.3)	66.5 (43.2 to 78.6)	65.8 (43.5 to 80.7)	68.3 (51.7 to 79.6)
Female/male ratio	57.0/43.0	59.2/40.8	51.6/48.4	62.7/37.3
Bleeding on brushing (n [%])	37 (27.6)	30 (29.1)	27 (42.2)	20 (40.0)
Education level (n [%])				
Low	39 (29.1)	28 (25.9)	17 (26.6)	19 (37.3)
Middle	73 (53.7)	67 (62.0)	34 (53.1)	20 (39.2)
High	23 (17.2)	23 (12.1)	13 (20.3)	12 (23.5)
BMI (kg/m^2; median [range])	26.3 (19.0 to 35.6)	26.4 (19.4 to 35.6)	25.3 (18.4 to 54.2)	25.5 (19.7 to 32.9)
Antibiotic intake (n [%])	28 (20.7)	24 (22.2)	9 (14.1)	10 (19.6)
hs-CRP (mg/l; median [range])	1.7 (0.2 to 14.1)	1.6 (0.1 to 15.8)	1.7 (0.1 to 17.6)	1.9 (0.2 to 16.6)
Plaque index (mean [SD])	1.5 (0.5)	1.5 (0.6)	1.7 (0.5)	1.6 (0.6)
Blood sugar (mmol/l; median [range])*	5.3 (4.3 to 6.4)	5.3 (3.5 to 6.3)	7.9† (4.8 to 18.9)	6.8† (4.2 to 18.9)
Control of blood glucose (n [%])				
<7 mmol/l			22 (34.4)	25 (49.0)
7 to 12 mmol/l			31 (48.4)	21 (41.2)
≥12 mmol/l			11 (17.2)	5 (9.8)
NIF intake (median [range])				
Daily dosage (mg)		20.0 (2.5 to 60.0)		20.0 (10.0 to 80.0)
Duration of intake (years)		6.5 (0.5 to 30.0)		5.0 (0.5 to 30)

* Kruskal-Wallis test showed a significant difference among the four subgroups (P <0.001).
† Mann-Whitney test showed a significant difference from NIF(–)/DM(–) and NIF(+)/DM(–) subgroups (P <0.001).

In the DM group with or without NIF intake (Table 2), there was a significant difference in the mean AL and PD, as well as the percentage of sites with AL ≥5 mm, AL ≥7 mm, and PD ≥4 mm. There was no significant difference in the number of missing anterior teeth or the percentage of sites with AL ≥3 mm or PD ≥6 mm.

Among the four subgroups, ANCOVA analysis showed that mean PD and the percentage of sites with PD ≥4 mm in subjects with NIF intake were significantly higher than in those without NIF intake. Patients in the NIF(+)/DM(+) subgroup had a higher percentage of sites with AL ≥5 mm (35.5%; 95% CI: 29.2% to 41.7%) than did those in the other three subgroups (24.7%, 95% CI: 20.8% to 28.7% for NIF[–]/DM[–], P = 0.004; 25.0%, 95% CI: 20.5% to 29.5% for NIF[+]/DM[–], P = 0.007; and 25.2%, 95% CI: 19.6% to 30.7% for NIF[–]/DM[+], P = 0.016).

Logistic regression analysis showed that the NIF(+)/DM(+) subgroup had a significantly higher risk for having more than 10% of sites with AL ≥5 mm with reference to the NIF(–)/DM(–) subgroup (odds ratio [OR] = 2.9; 95% CI: 1.2 to 7.4; P = 0.022), the NIF(+)/DM(–) subgroup (OR = 3.1; 95% CI: 1.2 to 8.1; P = 0.020), and the NIF(–)/DM(+) subgroup (OR = 5.1; 95% CI: 1.8 to 14.3; P = 0.002) (Table 3).

DISCUSSION

This study population was based on a cohort of urban community patients with essential hypertension, and all participants were non-smokers with no periodontal therapy in the last 6 months. In the present study, smokers were excluded rather than treated as a confounder that was subsequently subjected to statistical adjustment; this was strongly recommended in a review[25] on periodontitis–systemic disease associations. Then four subgroups of subjects with or without NIF intake and/or type 2 DM were recruited. To the best of our knowledge, this was the first study to investigate the possible association between NIF intake and periodontal destruction in DM.

It was noted in our previous study[26] of the same cohort that the prevalence of NIF-related gingival overgrowth was 7.3%, which may have contributed to increased PD.[2,27-29] It was confirmed in the present

Table 2.

Periodontal Conditions (mean [95% CI]) in Study Subjects (adjusted*)

Index	Non-DM Group		DM Group	
	NIF(−)/DM(−) (n = 135)	NIF(+)/DM(−) (n = 108)	NIF(−)/DM(+) (n = 64)	NIF(+)/DM(+) (n = 51)
Missing teeth (n)	1.1 (0.7 to 1.5)	1.6 (1.2 to 2.0)	1.4 (0.9 to 2.0)	1.9 (1.3 to 2.5)
AL (mm)	2.9 (2.6 to 3.1)	2.9 (2.6 to 3.2)	2.8 (2.5 to 3.2)	3.4 (3.0 to 3.8)†
Sites with AL ≥3 mm (%)	55.8 (51.5 to 60.1)	53.7 (48.8 to 58.6)	53.1 (47.1 to 59.2)	59.2 (52.3 to 66.0)
Sites with AL ≥5 mm (%)‡	24.7 (20.8 to 28.7)	25.0 (20.5 to 29.5)	25.2 (19.6 to 30.7)	35.5 (29.2 to 41.7)§
Sites with AL ≥7 mm (%)	7.7 (4.7 to 10.6)	9.4 (6.0 to 12.7)	9.0 (4.8 to 13.2)	14.7 (10.1 to 19.4)†
PD (mm)‡	2.3 (2.2 to 2.4)	2.5 (2.4 to 2.6)‖	2.3 (2.1 to 2.5)	2.6 (2.4 to 2.7)‖
Sites with PD ≥4 mm (%)‡	10.1 (7.4 to 12.9)	15.1 (12.0 to 18.2)‖	9.5 (5.5 to 13.5)	18.1 (13.6 to 22.6)‖
Sites with PD ≥6 mm (%)	2.0 (0.7 to 3.4)	3.3 (1.8 to 4.9)	1.5 (0.01 to 3.5)	3.2 (0.9 to 5.5)

* Age, gender, education level, BMI, antibiotics intake, plaque index, and SBI were adjusted with ANCOVA.
† Significant difference from the NIF(−)/DM(+) subgroup (P <0.05).
‡ Significant difference among the four subgroups (P <0.05).
§ Pairwise comparisons using the Tukey method showed a significant difference from NIF(−)/DM(−), NIF(−)/DM(+), and NIF(+)/DM(−) subgroups (P = 0.004, 0.007, and 0.016, respectively).
‖ Pairwise comparisons using the Tukey method showed a significant difference from NIF(−)/DM(−) and NIF(−)/DM(+) subgroups (P <0.05).

Table 3.

The Risk for More Periodontal Destruction (≥10% sites with AL ≥5 mm) in the NIF(+)/DM(+) Subgroup With Reference to the Other Subgroups in a Logistic Regression Analysis*

Subgroup	OR (95% CI)	*P* Value
NIF(−)/DM(−)	2.9 (1.2 to 7.4)	0.022
NIF(+)/DM(−)	3.1 (1.2 to 8.1)	0.020
NIF(−)/DM(+)	5.1 (1.8 to 14.3)	0.002

* Age, gender, education level, BMI, antibiotics intake, plaque index, and SBI were adjusted in a logistic regression model.

study that subjects with NIF intake exhibited significantly deeper PD and a greater extent of sites with increased PD than did those without NIF intake.

DM is a well-established risk factor for periodontal disease and tissue destruction. It was reported that patients with type 2 DM were 2.8 to 4.2 times more likely to have progressive periodontal disease compared to subjects without DM.[15,30-32] One meta-analysis[33] of four studies involving 3,524 patients found a two-fold higher risk for periodontal disease in those with DM. No information is available on whether NIF intake and DM increase the risk for periodontal attachment loss compared to DM alone. NIF intake might not only induce gingival overgrowth, especially in subjects with preexisting periodontal inflammation,[1,2] it could also affect bone metabolism[8,10,11] and enhance inflammatory infiltrate with a greater number of lymphocytes (especially B lymphocytes) in gingival tissues.[34] The present study showed that NIF intake was significantly associated with periodontal destruction in the DM group but not in non-DM group. DM and NIF intake significantly increased the risk for more attachment loss with reference to the counterparts without NIF intake, with an OR of 5.1 (95% CI: 1.8 to 14.3). These data implied that there might be a possible synergistic effect of NIF intake on periodontal pathogenesis in patients with DM. The explanation for this was hypothesized to be the similarity of the mechanisms that NIF and DM may be involved in the alteration of the host response in periodontal tissues as follows: NIF and DM can induce hyperresponsive monotype/macrophage phenotype, and thereby increase the production of chemokines and proinflammatory cytokines.[5,7,18,19]

A recent clinical study[27] showed that the interaction of CCB and other periodontal risk factors, such as tobacco smoking, may play an important role in periodontal pathogenesis, although the relevant mechanism remained unclear. It is likely that NIF intake may also interact with DM and thereby increase the risk for periodontal destruction. To some extent, the differences in periodontal destruction between patients with DM who did and did not have NIF intake

should be interpreted with caution because no detailed information on hypertension control and duration was collected from the subjects. Although there is no evidence that advanced hypertension could directly contribute to periodontal destruction in patients with DM, advanced hypertension requiring NIF medication might account for the results observed. Furthermore, the present study only examined the periodontal conditions in anterior teeth. Further studies should be extended to investigate full-mouth periodontal conditions and to elucidate the underlying mechanisms of DM and NIF intake interaction in periodontal destruction.

The present study did not find a significant difference in the extent and severity of periodontal destruction between NIF(–)/DM(–) and NIF(–)/DM(+) subgroups, which may have been due to the limited information available on the duration of DM and the current control status, with measurement of fasting blood glucose instead of glycated hemoglobin levels. It was well appreciated that the glycated hemoglobin level is a reliable index of the degree of DM control in the past 3 months. The present study should have included this parameter for the assessment of glucose levels and the generation of more meaningful data for group comparisons.

CONCLUSIONS

Elderly patients with DM may often have to take daily antihypertension medication, such as NIF. The current study suggested that NIF intake is an important risk factor for increased periodontal depths and increased the risk for attachment loss in patients with DM. From a clinical point of view, periodontal care is essential for patients with DM, especially those who take NIF on a daily basis, to achieve better management of periodontal disease. For these patients, emerging studies[15,35,36] showed that periodontal treatment might also contribute to DM control. This study suggested that NIF intake might significantly increase the risk for periodontal attachment loss in patients with DM. A long-term follow-up study is warranted to confirm the current findings.

ACKNOWLEDGMENTS

This study was supported by Capital Medical Development Fund (2003 to 2005) from the Beijing Municipal Health Bureau, Beijing, China. The authors report no conflicts of interest related to this study.

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Correspondence: Dr. Qingxian Luan, Zhongguancun S. Ave. 22, Haidian District, Beijing, China. Fax: 86-010-62173402; e-mail: luanqx@yahoo.com.cn.

Submitted January 16, 2008; accepted for publication April 19, 2008.