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Journal
Bulletin of Tokyo Dental College, 53(2): 91-99

URL
http://hdl.handle.net/10130/2831
Clinical Case Report of Long-term Follow-up in Type-2 Diabetes Patient with Severe Chronic Periodontitis and Nifedipine-induced Gingival Overgrowth

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Received 10 January, 2012/Accepted for publication 20 February, 2012

Abstract
In this case report, we describe the clinical course over a 14-year follow-up in a 47-year-old diabetes patient with severe chronic periodontitis and nifedipine-induced gingival overgrowth. The patient had a history of hypertension for over 5 years and uncontrolled type 2 diabetes. Overgrown gingiva was observed in most of the teeth and was marked in the upper and lower anterior teeth. A probing pocket depth of ≥4 mm and bleeding on probing (BOP) were observed in 94 and 90% of sites examined, respectively. At baseline, his hemoglobin A1c (HbA1c) was 8.5%. The patient received periodontal and diabetic treatment simultaneously. Medication was changed from nifedipine chloride to an angiotensin-converting enzyme inhibitor. After initial therapy and subsequent periodontal surgery, gingival overgrowth disappeared and probing depth and BOP showed a significant improvement. No recurrence was observed during supportive periodontal therapy (SPT). The HbA1c level improved from 8.5 to 6.3% after periodontal treatment, subsequently remaining at a good level during SPT over 10 years. This study demonstrated that periodontal treatment, withdrawal of medication and control of diabetes can result in remarkable improvements in type 2 diabetes patients with chronic periodontitis and nifedipine-induced gingival overgrowth. These results suggest that comprehensive periodontal treatment in combination with treatment for diabetes mellitus can exert a positive influence on blood glucose levels and periodontal condition in diabetic patients.

Key words: Chronic periodontitis — Nifedipine — Gingival overgrowth — Type 2 diabetes — Case report

Introduction
Poor metabolic control of diabetes mellitus (DM) has often been associated with severe periodontal disease18,21. Diabetes mellitus is a complex disease with both metabolic and
vascular components, and is characterized by hyperglycemia due to defects in insulin secretion or action or both. It is a systemic disease of the innate immune system \(^{11}\), and patients with DM are prone to severe periodontitis \(^{10}\), which is considered its sixth complication \(^{8}\). No significant differences were observed in the subgingival biofilm between periodontitis patients with or without DM \(^{20}\). Therefore, it was hypothesized that DM-induced exaggeration of host immune responses played a crucial role in periodontal pathogenesis \(^{10}\), as glucose-mediated advanced glycation end products can increase the production of proinflammatory cytokines and mediators, which could contribute to periodontal destruction \(^{22}\).

Periodontal disease may also affect blood glucose levels in diabetic patients through insulin resistance \(^{5}\). There has been a recent focus on understanding the negative influences of oral chronic inflammation on systemic health \(^{10,12}\).

Nifedipine, a dihydropyridine, is a calcium channel blocker that has been widely prescribed for various cardiovascular diseases, particularly hypertension \(^{3}\). The most prominent side effect of nifedipine therapy in oral tissue is gingival overgrowth \(^{9}\), which is characterized by an accumulation of extracellular matrix in the gingival connective tissue and epithelial hyperplasia with elongated, branched rete pegs penetrating deep into the connective tissue, with various degrees of chronic inflammatory infiltration \(^{1}\).

In this case report, we describe the clinical course over a 14-year follow-up in a 47-year-old type 2 diabetes patient with severe chronic periodontitis and nifedipine-associated gingival overgrowth. His diabetes and periodontal condition were evaluated longitudinally over 14 years.

**Case**

In September 1993, a 47-year-old man was referred to the Clinic of Conservative Dentistry at the Chiba Hospital of Tokyo Dental College with the chief complaint of gingival swelling around the upper and lower anterior teeth. The patient provided informed consent before entry into this study.

1. **Clinical Oral Examination**

Overgrown gingiva was observed at all the intradental gingival papillae in most of the teeth and was marked in the upper and lower anterior teeth. The consistency was generally fibrotic, with an erythematic appearance (Fig. 1). The patient stated that he first noticed the gingival enlargement approximately 6 months prior to the initial visit and reported rapid growth during this period of time. The maxillary and mandibular anterior teeth were flared out, and the patient had lost several teeth and had no prosthodontic treatment. The plaque control record (PCR) (O’Leary et al. \(^{13}\)) score was 85%. A probing pocket depth of \(\geq 4\) mm and bleeding on probing (BOP) were observed in 94 and 90% of sites examined, respectively (Table 1). Teeth with severe bone loss showed mobility ranging from 2 to 3 (Lindhe and Nyman \(^{7}\)). Radiographic examination revealed moderate horizontal alveolar bone loss, calculus, and localized severe vertical alveolar bone loss (#16, 17, 31, 37, 41, 42, 44, 45, 46) (Fig. 2).

2. **Systemic condition**

The patient’s weight was 80.2 kg and height 173.6 cm. Hypertension had been diagnosed 5 years prior to the patient’s initial visit and medication (calcium antagonist; nifedipine 40 mg/day) had been prescribed and taken for 18 months. Blood pressure was 135/85 mmHg. Two years prior to visiting our hospital, type 2 diabetes had also been diagnosed in this patient, who had been taking an oral antidiabetic agent (metformin, 500 mg/day) for 18 months. Further medical examination revealed uncontrolled type 2 diabetes. The hemoglobin A1c (HbA1c) value was 8.5%. No diabetic complications or history of smoking were found.

3. **Diagnosis**

Based on the clinical findings, a diagnosis
of severe generalized chronic periodontitis with gingival overgrowth associated with nifedipine was made. It was also considered possible that high blood glucose levels resulting from uncontrolled type 2 diabetes may have exacerbated periodontal inflammation.

4. Treatment
A collaborative dental-medical treatment plan was devised for diabetes-associated severe chronic periodontitis and nifedipine-induced gingival overgrowth.

First of all, a physician was consulted regard-

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Table 1 Clinical findings at baseline, after initial therapy and SPT

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Re-evaluation (After initial therapy)</th>
<th>SPT (0 y)</th>
<th>SPT (11 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of teeth</td>
<td>27</td>
<td>27</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mean probing depth (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 mm</td>
<td>6</td>
<td>34</td>
<td>98</td>
<td>100</td>
</tr>
<tr>
<td>≥4 mm, &lt;6 mm</td>
<td>18</td>
<td>27</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>≥6 mm</td>
<td>76</td>
<td>39</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding on probing (%)</td>
<td>90</td>
<td>23</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.5</td>
<td>6.5</td>
<td>6.3</td>
<td>6.3</td>
</tr>
</tbody>
</table>

*Percent of sites with indicated probing depth
Baseline, first visit (September 1993)
Re-evaluation (after initial therapy) (September 1994)
SPT (0 y): start of supportive periodontal therapy phase (January 1996)
SPT (11 y): (January 2007)
ing the patient’s uncontrolled type 2 diabetes and changes in dietary habits combined with an oral antidiabetic agent (metformin, 750 mg/day) were prescribed. The goal of dental treatment was to reduce periodontal infection and bacteremia, which may have affected the diabetic condition and gingival overgrowth, and to restore masticatory function, which may have affected dietary care for diabetes. Moreover, a physician was consulted regarding gingival overgrowth, which was a side effect of nifedipine, and whether it was possible to change the medication. The patient had been taking nifedipine for 18 months, but now the medication was changed to an angiotensin-converting enzyme inhibitor (enalapril maleate, 10 mg/day). Thus, treatment was restricted to periodontal therapy that mainly focused on plaque control until improvement of glycemic control. Treatment consisted of meticulous oral hygiene instruction and supragingival scaling. Pocket irrigation with 0.2% ethacridine lactate (acrinol®) was performed following the above procedures.

During the first 2 months on the new medication, gingival overgrowth gradually subsided. Tooth-brushing instruction resulted in an improvement in oral hygiene (PCR 19%). In March 1994, subgingival scaling and root planing were performed using Gracey curettes and an ultrasonic scaler as the baseline HbA1c (8.5%) had decreased to 6.9%. Although prognosis for teeth #16, 17, 27, 37, 44, 45, and 46 was judged to be hopeless, they were retained during initial therapy until HbA1c dropped to 6.5% or less.

In June 1994, the HbA1c decreased to 6.5% and these teeth were extracted with premedication using cephem antibiotics. A temporary prosthesis was applied.

In September 1994, re-evaluation was performed. The initial therapy resulted in an improvement in clinical parameters. Gingival inflammation, in particular, showed a significant reduction (BOP 23%, Fig. 3A, 3B, Table 1). Periodontal surgery (flap operation) was carried out between October 1994 and March 1995 in areas (teeth #11–15, 21–26, 31–34, 38, 41–43, 48) where probing depth was ≥5 mm and osseous defects were present. The flap operation was performed with premedication using cephem antibiotics. To prevent postoperative infection, cephem antibiotics (3 days) were prescribed and irrigation with 0.2% ethacridine lactate (acrinol®) performed frequently at the wound surface. Postoperative healing was uneventful. Re-evaluation after 3 months healing showed a marked improvement in clinical

Fig. 2 Dental radiographs at baseline
Generalized horizontal alveolar bone loss was observed. Advanced bone loss was observed at lower incisor, molar and upper right molar.
parameters (Fig. 3C). A reduction in probing depth was obtained at all the surgically treated sites. A removable partial denture was applied to the right-side maxillary posterior area (#16, 17) and bilateral mandibular posterior area (#35–37, 44–47, Fig. 3D). The upper and lower anterior teeth were fixed and restored by using a hard resin facing crown (#11, 12, 21, and 22, and #31, 32, 33, 41, 42 and 43, Fig. 3D).

5. Supportive periodontal therapy

After surgery and prosthodontic treatment, the patient was placed on a supportive periodontal therapy (SPT) program, consisting mainly of oral hygiene instruction and professional plaque control once a month. Changes in periodontal condition and HbA1c are shown in Figs. 4, 5, 6. Assessment was performed based on the method of Shimoe et al.\textsuperscript{17}. Gingival inflammation was resolved (Fig. 4), and all sites had probing pocket depths $\leq 3$ mm (Table 1). Radiographic examination clearly revealed lamina dura in the alveolar bone (Fig. 5). The patient was motivated to maintain daily plaque control (average PCR, 19%), and his systemic and oral condition remained good for 11 years following commencement of SPT (Fig. 6). The baseline HbA1c value (8.5%) decreased to 6.3% after periodontal surgery. The HbA1c value ranged from 6.3 to 6.5% during SPT (Fig. 6). The patient remained on the same medication for his systemic condition for 14 years from baseline. Blood pressure remained within the normal range during the observation period.

Discussion

This case report demonstrated the successful recovery and maintenance of healthy periodontal conditions over a 14-year period.
following a diagnosis of nifedipine-induced gingival overgrowth in a patient with diabetes and advanced chronic periodontitis. Moreover, the patient’s HbA1c level improved from 8.5 to 6.3% after periodontal treatment, subsequently remaining at a good level during SPT over a 10-year period. The present findings agree with data previously reported in treatment and maintenance studies of short duration\textsuperscript{20}. Controlled studies have shown that the response of diabetics to non-surgical and surgical periodontal therapy is similar

Fig. 4 Oral photographs during supportive periodontal therapy
Gingival redness and swelling had disappeared. A prosthetic denture was applied to replace upper and lower teeth.

Fig. 5 Dental radiographs during supportive periodontal therapy
Crestal lamina dura was clearly visible at interproximal sites in the alveolar bone.
to that of non-diabetics. On the other hand, it was reported that poorly controlled diabetics respond less successfully to periodontal therapy relative to well-controlled and non-diabetics. Tervonen and Karjalainen reported that although poorly controlled diabetics responded to nonsurgical therapy similarly to controls in the short term (4 weeks), in the absence of maintenance therapy, more rapid recurrence of periodontal pockets and subgingival calculus was found. The data from the present study, however, seem to indicate that careful control of disease in patients with diabetes will result in a similar low frequency of recurrent periodontitis to that seen in non-diabetic patients if they receive treatment for periodontal disease and follow a careful plaque control program. These findings suggest that information on the level of glycemic control in diabetics is useful in determining periodontal prognosis and the need for periodontal therapy on an individual basis. Therefore, assessment of metabolic status is important in determining the prognosis and recall interval for periodontal therapy.

In the present case, the patient’s HbA1c level showed a marked improvement from 8.5 to 6.3% after periodontal treatment. Much evidence indicates a bidirectional relationship between diabetes and periodontal disease. It is possible that periodontitis plays some role in the development of insulin resistance. Iwamoto et al. reported that antimicrobial periodontal therapy was effective in improving metabolic control in diabetics, possibly through reduced serum TNF-α and improved insulin resistance. The authors also suggested that increased TNF-α caused by chronic inflammation may have an additive effect on insulin resistance in type 2 diabetes patients. This indicates that controlling periodontal infection would play an important role in the overall management of this disease. However, to date, relatively few intervention studies have examined the effect of periodontal therapy on the metabolic status of diabetes. Therefore, there is no consistent agreement as to the beneficial effects of periodontal treatment on the metabolic control of patients.
with diabetes. In the present case, too, it is unclear as to the precise reason for the observed improvement in the patient’s diabetes, as periodontal and diabetic treatment were performed simultaneously. The improvement in HbA1c level may have been due to the improvement in insulin resistance following reduction of circulating levels of several proinflammatory cytokines, which is probably associated with the effect of periodontal treatment. Moreover, periodontal treatment including restoration of masticatory function appears to affect dietary care for diabetes.

In this case, the withdrawal of medication and removal of plaque provided relative resolution of gingival tissues. Earlier reports on treatment for nifedipine-induced gingival overgrowth involved reduction or elimination of the drug or surgical excision. It was reported that the presence of dental plaque and inflammation might be a significant risk factor for gingival overgrowth. We emphasized plaque control as the first step in our treatment program and during SPT. A recent study on patients with type 2 diabetes showed that nifedipine intake was associated with a significantly deeper probing depth and greater extent of sites with increased probing depth. It remains unknown as to whether hyperglycemic status and its effects on gingival tissue play a synergistic role in drug-influenced gingival enlargement. This study demonstrated that withdrawal of medication and control of diabetes resulted in remarkable improvements. Further controlled investigations should be carried out to further clarify this possible complex interaction.

In summary, this study demonstrated that periodontal treatment, withdrawal of medication and control of diabetes can result in remarkable improvements in type 2 diabetes patients with chronic periodontitis and nifedipine-induced gingival overgrowth. These results suggest that comprehensive periodontal treatment in combination with treatment for diabetes mellitus can exert a positive influence on blood glucose levels and periodontal condition in diabetic patients.

**Acknowledgements**

We would like to thank Associate Professor Jeremy Williams, Tokyo Dental College, for his assistance with the preparation of this manuscript.

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